An ENDOCRINE HANDBOOK

By
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OUTLINE OF CONTENTS

THE PUBLISHERS' PREFACE

THIS ENDOCRINE HANDBOOK is an attempt to inform our friends of the trends of progress in endocrine therapy, particularly those everyday phases of the subject upon which our work is based. It is not intended to be a review of glandular physiology or pathology, nor is it a treatise on the clinical aspects of endocrine or near-endocrine disorders.

There is indeed a plethora of material on endocrine therapy. While one dislikes to omit so much of interest, consideration cannot be given in this limited space to every source of potentially valuable glandular products. Discussion of some glands is omitted (e.g., pineal, thymus); others do not receive the attention that their importance in current medical literature seems to warrant. For example, the chief hormones from the pancreas and parathyroids (insulin and paroidin) are not discussed because they are process-patented products. A number of endocrine principles that are not generally available to the profession (e.g., inhibin, folliculin, kallikrein, corporin) are dismissed with meager mention, for other preparations either are identical with them or have similar therapeutic potentialities.

For purposes of expediency we were forced to consider in some chapters matters that properly belonged elsewhere. For instance, mammary therapy is considered under luteal therapy, for these two forms of antiovarian organotherapy are cooperative, perhaps even related. Again, the placenta for a long time was the source of an "ovarian" or estrogenic product (Plestrin), but this is considered under Ovarian Therapy (Chapter VI). Then, too, the anterior pituitary hormones are no longer always obtained from pituitary glands; indeed, there is a "twin" which has so much in common with the earlier antepituitary extracts that it is called the anterior pituitary-like (A.P.L.) hormone. This also is discussed in Chapter VI.

The reader will be able quickly to find much practical information that can be utilized in his work. While the manuscript for this book was being prepared, it occurred to the author that pointed excerpts from current medical literature might be given as more direct evidence of the validity of many views that are outlined here. These "Clinical Excerpts," which follow each chapter, constitute an exceptionally valuable review of the subjects considered, and the index makes this therapeutic information much more accessible.

The Harrower Laboratory publishes a quarterly house organ, The Hormone, and a monthly sheet, The Endocrine News Letter, which are the channels through which we pass along to our friends information on the recent advances in this field. Either or both of these will be sent to interested physicians on request.

It may be added that we have no interest whatever in dealing directly with the laity; The Harrower Laboratory makes no use of the lay press; and every attempt is made to conserve the high ethical standards to which we have adhered these many years. Correspondence with the profession is welcomed, and to them we pledge our best efforts.

THE HARROWER LABORATORY, Inc.

Vice-President
and General Manager
April, 1939
Glendale, California

I.—AN INTRODUCTION TO ORGANOTHERAPY

THE AIM of The Harrower Laboratory from its inception twenty-one years ago has been "to develop information pertaining to the internal secretions in general practice and to perfect the means whereby this information can be applied." Today endocrinology and its corollary, organotherapy, are more firmly established than ever. We believe we have had a small part in this, and we are justly proud of it.

Endocrinology in Everyday Medicine

WHEN our first noteworthy printed effort was issued in 1921 (the 400-page book, "Practical Organotherapy: The Internal Secretions in General Practice," which to our surprise ran into four editions with a total publication of 65,000 copies), some of our friends objected that, while the book in itself might be pretty good, "Harrower was trying to make endocrinologists out of every Tom, Dick, and Harry in the profession." I couldn't make up my mind whether to resent this or not, but the more I thought of it, the more it seemed to be an unintended compliment, for are not the Toms, Dicks, and Harrys in medicine the oft-forgotten yet truly important figures in maintaining the public health?

The idea that endocrinology should be the private preserve of a small group has always seemed wrong to me. To be effectively treated, endocrine disorders must be seen and recognized early, and the doctor in the best position to do this is surely the general practitioner. There are, of course, problem cases that need special consultation, and it would be naive to believe that every physician could be an endocrinologist. But all can be made aware of the clinical aspects of the common endocrine disorders, and should be able to recognize early dyscrinisms and recommend suitable therapy before the lesions become advanced or irreversible.

Pluriglandular Therapy

IN the days when single-gland medication was a sort of obsession with some, considerable space and no little vehemence were used in criticizing pluriglandular therapy, or "shotgun formulas," as they were sometimes called. In its proper place a shotgun is the most reliable and effective weapon, but it is not the only weapon. So, in organotherapy, pluriglandular formulas are not always indicated. But, because the family of glands is closely interrelated, it is difficult to hurt one member without injuring others. The pluriglandular idea today has many staunch friends who know its therapeutic value as well as its rationale. As the Editor of the Prescriber (Edinburgh)[1] aptly puts it:

"Pluriglandular therapy, while still widely practised with considerable success, is undergoing a change of front. It is as unjustifiable to condemn it wholesale as it is to practise it blindly. More than one eminent endocrinologist has recently admitted that certain glandular preparations often act better when combined with thyroid."

Oral Organotherapy

THERE was a time when it was fashionable to believe that no glandular product "with the exception of thyroid, of course," was effective by mouth. To take this position now would be to ignore hundreds of excellent clinical and experimental reports to the contrary, many of which are cited in this book. This misconception is typical of other mental attitudes that have frequently delayed the acceptance and application of therapeutic advances. A rather amusing example of this was confessed recently by Sir W. Langdon-Brown.[2] In his address, "The Dead Hand in Medical Science," Sir Walter tells of his own original inability to believe that liver feeding could be an effective treatment of so serious a disease as pernicious anemia:

"I record it to my shame, however, that when Prof. A. V. Hill wrote from the United States to tell me of the extraordinary results which were just beginning to be obtained from liver treatment, I wrote back, 'Wonderful men, these Americans; do they give bacon with their liver?' "

But a Nobel Prize in medicine was awarded in 1934 for this outstanding organotherapeutic attainment. This, by the way, was the second Nobel Prize for accomplishments in endocrine therapy. (The other was given in 1923 for insulin.)

Misconceptions about Organotherapy

A NUMBER of unfortunate misconceptions about organotherapy have penalized many a physician who has been led to accept them. For instance:

Rarely does any form of glandular therapy in itself cure disease. Even the literally miraculous effects of thyroid in myxedema or cretinism, and insulin in diabetes mellitus, usually must be supplemented with non-endocrine measures, and the substances must be given continuously.

Now that numerous endocrine active principles, both natural and synthetic, are available, we occasionally hear statements derogatory to the older forms of organotherapy. Sevringhaus [3] hints of this in his recent book, thus:

"Since we can now have an extract with tested potency for every gland action which is demonstrable in the human, there is no need to prescribe any hormone other than one of known chemical purity or in a standardized extract of labeled potency."

Analyzed carefully, parts of this statement might be debatable, but all of us will agree upon the desirability of purification, potentiation, and standardization of glandular extracts. The error lies in interpreting statements such as this to mean that the clinical value of a product is in direct proportion to its chemical purity; that the newest method of standardization is the best; and that less pure or imperfectly standardized extracts should be abandoned forthwith. Such an attitude is demonstrably unsound, yet endocrine history has many examples of excellent minds who have clung to it for a time with a curious high-minded intolerance.

Twenty-five years ago when thyroxin was triumphantly separated from the thyroid gland, crude thyroid extract was renounced by many as an un-

scientific product. Today this situation is entirely reversed and an almost negligible quantity of thyroxin is used in practice. (See Chapter III.) By this, it is not intended to discount the advances with the separation or synthesization of endocrine-like active principles, most of which, by the way, are recorded in the Appendix (page 113). There is another side, however, which is suggested by Harvier [4] of Paris. In his recent review of progress in endocrinology, after expressing some thoughts on the relative merits of single hormones and whole glands as therapeutic agents, he says:

"Furthermore, just as the alkaloid does not always possess all the characteristics of the plant from which it is obtained, so the hormone does not always contain all the qualities of the gland from which it was originally isolated. Quinine is not cinchona, any more than morphine is opium; thyroxin is not thyroid extract; nor is epinephrine the adrenal extract. Just as it has not been demonstrated that morphine, as such, exists in gum opium (since the product may possibly be the result of manipulation of the plant), so no proof exists that there is a complete identity between the synthetic crystalline hormone and the natural hormone which is manufactured by the endocrine gland itself."

It is a truism, of course, that some glandular substances, such as epinephrine or insulin, are relatively ineffective when given by mouth. However, thyroid protein is extremely effective by mouth even though it is inactivated by enzymic activity. This is due apparently to the fact that enzymic inactivation may be reversible—that the very enzymes that digest hormone proteins may be capable of recombining the fragments by "enzymic synthesis." Wilson, Sappington, and Salter [5] point out that a number of investigators have obtained positive results even with orally administered insulin. By varying the insulin protein in different ways, these workers were able to obtain consistent hypoglycemic effects in animals. They conclude:

"These observations suggest qualitative similarities between thyroglobulin and insulin with respect to the action of proteolytic enzymes. They suggest, further, that hormonal proteins can be used orally under suitable conditions."

Certainly work of this kind suggests that future progress in hormone therapy may be not only in the perfection of synthetic substances but also, probably with more practical value, in the potentiation of glandular extracts for oral use by improved methods of production and standardization.

Certain glandular fractions are used in the treatment of conditions that can be ameliorated but not basically changed. Anabolin, the hepatic depressor fraction, which is used quite effectively in functional hypertension, has no effect on sclerotic vascular changes or renal degeneration, both of which often complicate the ordinary cases of high blood-pressure. Again, Panocrin-C, the tissue extract containing the so-called "circulatory hormone" of the pancreas, is used to modify certain aspects of well-advanced circulatory diseases, such as gangrene, angina pectoris, and intermittent claudication. Obviously, the serious and ultimate pathologic changes present in such conditions cannot be expected to be removed by any remedy. Pancreas tissue extract does not

eradicate the disease for which it is given, but neither do the nitrites, morphine, and many other useful drugs.

The Response to Endocrine Remedies

JUST as it is wrong in questions of etiology to assume that all diseases have a single cause, so in glandular therapy it is a fallacy to assume that all glandular products have a single mode of action. Endocrine remedies usually are given with one or more of four types of responses in mind:

1. Substitutive organotherapy, or replacement therapy, as with thyroid feeding in the functional as well as the organic type of hypothyroidism; or as with Plestrin, given to raise the estrin level of the blood.

2. Homostimulative organotherapy, as when glandular therapy is given to facilitate the reestablishment of a functionally depleted glandular mechanism. This therapy is based on Hallion's [6] law, which states:

"Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favors its restoration."

3. Pharmacodynamic organotherapy, as when endocrine principles are given for their direct or specific and essentially drug-like effects, e.g., epinephrine in asthma or shock, and the postpituitary oxytocic hormone when used during labor.

4. Empirical organotherapy, or the use of glandular preparations because they are reported to have been used in certain conditions with real benefit but without complete corroborative proof of value.

Many examples of all these forms of therapy are given in these pages, and this handbook is an attempt to bring such information up to date for the convenience of those who wish to utilize it. Naturally we hope that this collection of material may not only arouse renewed interest in the things we are doing in the field of endocrine therapy and the basic endocrine verities, but that it may help to lay at rest a number of misunderstandings that die hard. To the many friends who have honored us with their good-will throughout the years, I dedicate this little effort.

Henry R. Harrower

1. Editorial: Prescriber, May, 1938, xxxii, 125.
2. Langdon-Brown, Walter: Lancet, Jan. 29, 1938, ccxxxiv, 277.
3. Sevringhaus, E. L.: Endocrine Therapy in General Practice, 1938, p. 19.
4. Harvier, P.: Clin. Med. and Surg., Jan., 1939, xlvi, 18.
5. Wilson, H., et al.: Endocrinology, Nov., 1938, xxiii, 535.
6. Hallion, L.: Presse med., 1912, xx, 433.

II.—ADRENAL THERAPY

THERE is no more dramatic chapter in modern endocrinology than the progress made in our knowledge of the functions of the adrenals. From its inception, The Harrower Laboratory has taken a leading part in the investigation and application of adrenal therapy. In fact, this was one of the chief reasons for founding this institution.

In 1913 the writer became convinced of the value of adrenal support in many common asthenic syndromes from observing the work of Emile Sergent, the great French clinician. As early as 1898 Sergent described the two prime functions of the adrenals—antitoxic and angiotonic. His description of the detoxicating function of the adrenals was vivid, as will be seen by reading his book, "Etudes cliniques sur l'insuffisance surrenale," from which the following is translated (page 24):

"Should these glands happen to be damaged . . . a condition of depression and muscular fatigue is seen to appear which, in man, we shall find in the form of the earlier symptoms of adrenal insufficiency—asthenia."

While Sergent did not understand the exact mechanism of the action of the adrenal hormones, his clinical observations accurately anticipated the most modern views. So did those of the late C. E. deM. Sajous, one of the American pioneers in endocrinology, whose views closely paralleled those of Sergent. Sajous[1] was well aware of the practical importance of adrenal support, and described the syndrome of minor adrenal insufficiency thus:

"Functional hypoadrenia is the symptom-complex of deficient activity of the adrenals due to inadequate development, exhaustion by fatigue, senile degeneration, or any other factor which, without provoking organic lesions in the organs or their nerve-paths, is capable of reducing their secretory activity. Asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anaemia, slow metabolism, constipation, and psychasthenia are the main symptoms of this condition."

The Cortico-Adrenal Hormone (Adreno-Cortin)

MUCH of the criticism of Sergent, Sajous, and other pioneers stemmed from the quite fallacious assumption that the adrenal internal secretion was epinephrine. Strangely enough, although the cortex hormone (cortin) is essential to life and far transcends in importance the medullary hormone, it was not discovered until more than twenty-five years after epinephrine. With the separation of cortin and its de-epinephrinization came a profound change in attitude toward adrenal therapy. Hypoadrenia is now recognized as a cortical, not a medullary, deficiency. There is now a firm scientific basis for the control of minor adrenal insufficiencies with cortex therapy, and the cortex preparations of today are so potent as to be capable of maintaining life in bilaterally adrenalectomized animals.

Kendall[2] believes that the cortex hormone is probably a double bond unsaturated ketone, though the precise chemical structure has not yet been

determined. In England a synthetic product—desoxycorticosterone acetate—is under test. (See Appendix, Section 2.)

The manifold and vital functions of the cortex are best indicated by the changes that follow experimental adrenalectomy. These are chiefly a lowering of the body temperature, gradually increasing muscular weakness (asthenia), anorexia, hemoconcentration (resulting in lowered blood-pressure), dehydration, disturbances of the sodium-potassium balance (loss of salt, rise in blood potassium), retention of nitrogen, and a gradual hypoglycemia. Clinically, these reactions are found in ultimate degree in Addison's disease, and one or more of them are usually seen in the lesser degrees of adrenal insufficiency.

Sub-Addisonian Adrenal Insufficiency

SOME years ago (1936) the Harrower organization published a brochure entitled "Minor Adrenal Insufficiency as a Major Clinical Problem." The validity of this conception is borne out by many later publications. For instance, in his recent and very conservative book, Sevringhaus[3] remarks:

"There are probably many more cases with hypoadrenal activity of chronic types, in which the diagnosis of Addison's disease is not justified by conventional usage but in which the fundamental difficulty is similar but less marked. No definite diagnostic terminology or criteria are accepted for such cases. They are being increasingly considered as mild hypoadrenia."

Recent reports by Reed,[4] Steinfield,[5] Kemp,[6] Hartman,[7] and others are in line with this suggestion that a sub-Addisonian degree of adrenal insufficiency is the underlying mechanism of a large variety of hitherto baffling syndromes. For example, Reed[4] states that

"The clinician sees, not infrequently, patients who complain of asthenia, anorexia, easy tiring, palpitation, languor, variable abdominal pains, often unexplained nausea, vomiting and diarrhea, with no evident reason apparent on physical examination. Various functional symptoms are present. The systolic blood-pressure is below normal. The basal metabolism is little, if any, depressed. Careful search for psychogenic factors is unrewarded. The organic structure shows no constant abnormalities, and the diagnosis of neurasthenia often seems inevitable and equally unsatisfactory. . . . It seems logical to expect that adrenal deficiency may exist in all degrees short of the picture of Addison's disease, and that such deficiency may follow other causes than organic destruction of cortical substance."

In his closing remarks this author emphasizes the diagnostic value of organotherapy in the less easily recognizable endocrine disorders, a matter which is given further consideration in the chapter on thyroid. His conclusions follow:

"(1) Subclinical Addison's disease, or various stages of adrenal insufficiency, are seen clinically. (2) Such cases do not always exhibit all the symptoms of adrenal insufficiency, so that response to treatment becomes of diagnostic value."

The treatment recommended by Reed is adrenal cortex extract by mouth or by injection or both, together with an adequate intake of common salt and a diet low in potassium.

More specifically, many of the clinical reports have shown the importance of cortex therapy in asthenia, neurasthenia, myasthenia, and other "fatigue syndromes," pernicious vomiting of pregnancy and other pregnancy toxicoses, certain acute infectious states, and the convalescence which follows them, hyperthyroidism, surgical shock, and the toxemic shock of extensive burns.

Such a wide variety of indications is based upon the three main actions of the cortex hormone postulated by Steinfield and his associates.[5]

(1) Its relation to the mineral metabolism; (2) its interrelationship with other hormones—the part played by the adrenals in pluriglandular syndromes; (3) its close association with the immune processes, vitamin metabolism, etc. There can be no question that many patients are still being neglected or misdiagnosed because of the widespread attitude that the only adrenal deficiency is Addison's disease. As these same writers put it:

". . . the whole subject has become so well defined that it is now possible to recognize subclinical or mild types of Addison's disease by definite even though slight chemical alterations. This phase in itself has greatly enlarged the clinical outlook at first restricted to the rather small group of fully developed Addison's disease. These individuals go about in a constant state of ill health without episodes severe enough to cause hospitalization and without a clear-cut diagnosis."

Steinfield calls attention also to a clear example of the interrelationship of the adrenals with the pituitary and gonads—Simmonds' disease. As with Addison's disease, a patient with advanced Simmonds' cachexia is a rare and interesting pathological specimen for whom little can be done. But these investigators now believe that this pluriglandular syndrome may be recognized in its incipiency, and they describe two cases in which dramatic improvement followed cortex therapy.

Importance of the Cortex Lipid (Cortinoral)

IT is not surprising to find the adrenals involved in so many and varied syndromes when we recall their importance, as originally shown by Walter B. Cannon, in the body's adaptation to mental, emotional, physical, and infectious traumas. Quite recently Selye,[8] in his studies on adaptation, illuminated our knowledge of the "alarm reaction" by demonstrating histological effects upon the adrenals of animals exposed to cold, traumatic injuries, excessive muscular exercise, spinal shock, acute infection, and drug intoxications. The most striking phenomenon was the rapid disappearance of the lipid granules in the adrenals, which gradually reappeared at the end of the "alarm" stage, or when adaptation was attained.

This confirms some work done during the war when the great influenza epidemic caused many deaths in the camps. Lucke and his associates[9] at Camp Zachary Taylor, reported 126 cases coming to autopsy and noted how routinely the adrenals were damaged. Quoting from their report:

"In three instances frank hemorrhages in the suprarenal substance, enlarging the organ to about twice its normal size, were present. In 20 cases the

suprarenal showed no gross changes. In the remaining 103 cases there was slight increase in size and definite congestion. . . . Microscopically, . . . the cells of the cortex appeared slightly swollen and usually devoid of their lipoid granules. This lipoid exhaustion was observed almost constantly."

It seems that the adrenal cortex produces more than one hormone and that these glands are closely concerned with the immunity responses. There are several hints of this in the literature. For instance, S. Levy Simpson[10] stresses this important factor in the body's defense against infections:

"Experimental and pathological evidence indicate that the adrenals play a part in the reaction to infection. Probably both medulla and cortex participate, but the cortex tends to show more obvious changes. Thus, there is a decrease of lipoid, a vacuolization of cells, degeneration of nuclei, vascular engorgement, and a liability to haemorrhage and thrombosis. . . . Adrenalectomized animals, and also patients with Addison's disease, are susceptible to intercurrent infection, and their resistance to infection is so poor that a comparatively trivial infection may lead to death."

We know now that the cortical hormone is intimately attached to the lipids of the adrenal cells and can best be extracted with lipid solvents. The newest (1937) Harrower cortex product, Cortinoral (page 22), is a lipid extract biologically assayed by feeding tests on animals to contain a definite physiological unitage per capsule. (See Appendix, page 116.) It is capable of maintaining life in adrenalectomized animals, which confirms not only its nature and potency, but its efficacy when given by mouth. Properly prepared extracts of the adrenal cortex actually may be more potent given orally than parenterally. In this connection, Grollman[11] states:

"If one compares the effects of a single parenteral injection with the results which follow the administration of the hormone in the animals' food, one finds that the oral method of administration yields better therapeutic results than the parenteral administration of the same dose of the hormone."

A number of articles have been published by the Pottengers confirming the value of oral adrenal cortex therapy, particularly in asthma. For example, in one of their most recent papers[12] they report a series of fifty allergic asthmatic children under treatment for a year. Whole adrenal gland was found to be more effective than epinephrine, and most satisfactory when given in conjunction with a high salt intake (1 tsp. in a glass of water t.i.d.). As many as 84 per cent. of these children were improved, and the broader endocrine value of such treatment was seen in the coincidental physical improvement and the fact that in six cryptorchid boys in this group of fifty, descent of the testes occurred in all.

Since 1929 The Harrower Laboratory has been offering an epinephrine-free aqueous cortico-adrenal extract, Sol. Adreno-Cortin (page 22), the potency of which is demonstrated by biological tests on bilaterally adrenalectomized animals. (See Appendix, page 116). This solution is given by parenteral injection, the usual dose being from 1 to 3 cc. daily or more frequently. In Addison's disease 5 cc. or more is advisable; sometimes at the beginning of treatment as much as 20 cc. is given during twenty-four hours. Adreno-Cortin (page 22) is also available in capsules for supplementary use.

The Broader Value of Adrenal Support with Adremin

RECOGNIZING the importance of the adrenals in the regulation of many vital body functions, the frequency with which the chief manifestation of hypoadrenia (asthenia) occurs in such a large number of syndromes; recognizing also the close relationship of the adrenals to other glands, particularly the thyroid, pituitary, and gonads, The Harrower Laboratory in 1918 offered a tonic pluriglandular formula (Adreno-Spermin) now known as Adremin (page 23). This formula, consisting of adrenal cortex, thyroid, and gonad extracts, was recommended as a means of "adrenal support," or as a physiologic opponent to the endocrine accompaniments of fatigue. When, a few months after its introduction, the great influenza epidemic swept the world, this formula was found to be unusually effective in overcoming many of the asthenic, hypotonic, depleted states that were such common and serious sequelae of this particular infection. This coincidence not only drew attention forcefully to the practical value of this formula, but made many physicians aware that the ultimate text-book endocrine diseases, while they provide the best possible examples of endocrine pathology, do not always present the most promising opportunities for therapy. Naturally, the early functional endocrine disorders are infinitely more common and far more likely to respond to glandular therapy.

An editorial in the Prescriber [13] some years ago (1923), contained a statement which, considering the remarkable progress that has been made during the years that have intervened, is still surprisingly apropos:

"The ordinary hypoadrenia described by Sergent is purely functional in character; it follows toxaemias of various origin and is a frequent sequel to many everyday medical experiences. It is here that adrenal therapy has its place. The causal toxaemia having been neutralized and the factors which deplete the adrenals having been controlled, some form of adrenal encouragement—designated by Harrower 'adrenal support'—must be resorted to. This means administration of gland substance, for, just as cases of hypothyroidism respond to treatment with dried thyroid, so does functional hypoadrenia call for some kind of adrenal feeding."

The widespread medical, as well as social, aspects of adrenal insufficiency are being considered as never before, and organotherapy is being recommended as a solution of this problem. In a Paris Letter to the Journal of the American Medical Association [14] a writer refers to the medicosocial aspects of hypoadrenia and concludes:

"It is of the utmost importance for the educator and social worker to keep these two types in mind and not to ascribe the desire to avoid physical or mental effort to laziness or lack of ambition. The treatment is preventive and includes a mode of living in which there is as little excitement as possible, an ample and carefully selected diet, and the administration of adrenal preparations, combined or not, according to the individual case, with the use of ovarian or testis prescriptions and vitamin C."

Adremin, then, represents a basic triune principle in the pluriglandular therapy of functional adrenal insufficiency, and in most cases the combining

of these extracts of related glands to restore the kinetic control is definitely an advance over adrenal therapy alone or thyroid therapy alone. When single-gland adrenal-cortex therapy is desirable, Sol. Adreno-Cortin (the first biologically standardized cortex solution to be made available to the profession) and/or Cortinoral by mouth, both potent standardized products, may be used.

The Adrenal Medullary Hormone

A LONG chapter could be written about the adrenal medullary hormone, the essentially pharmacodynamic pressor agent—adrenalin or epinephrine. Since 1900 it has revolutionized the control of asthma, anaphylaxis, and shock. Its topical use in congestive and hemorrhagic conditions is equally remarkable, and it is now a part of the armamentarium of every physician.

Until recently this exceptionally potent endocrine principle—a dilution of as low as 1:3,000,000 of epinephrine hydrochloride is capable of demonstrating its remarkable pressor potency—was given hypodermically, from 3 to 10 min. of the 1:1,000 solution sufficing for the control of asthma paroxysms. But within the last three years a new mode of administration has been developed which confers a genuine boon on sufferers from certain allergic disorders.

It is now possible for the asthmatic largely to avoid the inconvenience of the hypodermic needle. A 1 per cent. isotonic solution of epinephrine (Endophrin Inhalant—Harrower) is inhaled through the mouth, in most instances a few inhalations taking the place of an injection. This new procedure may, as Graeser and Rowe [15] put it, "be widely substituted for the hypodermic administration of adrenalin."

As epinephrine solutions are quickly spoiled by contact with metal, an all-glass nebulizer is essential. Since only from 3 to 10 min. is required at a time, an exceptionally small apparatus is desirable. The Harrower Endophrinizer (described on page 23) was designed especially to meet these needs.

1. Sajous, C. E. deM.: The Internal Secretions and the Principles of Medicine, 1920, Vol. 1, page 83.
2. Kendall, E. C.: Trans. Assn. Am. Phys., 1934, xlix, 147; ibid., 1937, lii, 123.
3. Sevringhaus, E. L.: Endocrine Therapy in General Practice, page 140. (See Appendix.)
4. Reed, Alfred C.: California and West. Med., May, 1937, xlvi, 308.
5. Steinfield, E., et al.: Jour. Lab. and Clin. Med., Jan., 1938, xxiii, 329.
6. Kemp, W. N.: Can. Med. Assn. Jour., April, 1933, xxviii, 389.
7. Hartman, F. A., et al.: Endocrinology, July, 1937, xxi, 516.
8. Selye, Hans: Endocrinology, March, 1937, xxi, 169.
9. Lucke, B., et al.: Arch. Int. Med., Aug., 1919, xxiv, 154.
10. Simpson, S. L.: Practitioner, Jan., 1938, cxl, 28.
11. Grollman, Arthur: The Adrenals, page 260. (See Appendix.)
12. Pottenger, F. M., Jr., and Pottenger, F. M.: California and West. Med., Oct., 1938, xlix, 271.
13. Editorial: Prescriber, May, 1923, xvii, 167.
14. Paris Letter: J.A.M.A., Feb. 11, 1939, cxii, 564.
15. Graeser, J. G., and Rowe, A. H.: California and West. Med., Aug., 1935, xliii, 110.

ADRENALS—CLINICAL EXCERPTS

Asthenia, Circulatory Weakness.—. . . In addition to Addison's disease there are a number of conditions of lowered blood-pressure, asthenia, and circulation weakness . . . which are regarded by some as the result of hypofunction of the suprarenals. In these conditions, excellent results are reported from giving gland substance.—H. A. Christian, J.A.M.A., Nov. 15, 1924, lxxxiii, 1588.

Asthenia: Nervous, Muscular, Circulatory.—Two clinical types of adrenal insufficiency are recognized: first, functional insufficiency; and second, the insufficiency based upon pathological changes found in the adrenals. . . . Because of the muscular, nervous and circulatory asthenia and loss of appetite, following infections such as scarlet fever, diphtheria, pneumonia, influenza, focal infections, etc., and at times occurring independently of such infectious processes, it has been frequently postulated that adrenal insufficiency must exist. French clinicians, especially of the military, have written much regarding an exhaustion syndrome in soldiers which they attribute to hypoadrenia.—A. A. Werner (Book, see Appendix) page 475.

Asthenia (Fatigue Syndrome).—Fatigue, as we see it today, is an expression of under- or exhausted functioning of the so-called endocrine chain of glands or tissues; and the rational treatment of psychophysical fatigue is the employment of associated ductless gland substances as they seem to be physiologically associated in the living normal organism. . . . With our present partial knowledge of the functioning of the endocrine chain of glands, it appears as though the suprarenals were the first to show signs of fatigue, for the simple reason that they seem to have most of the work to do in the autoprotective function.—J. McNulty, New York Med. Jour., 1921, cxiii, 288.

Asthma.—A crude extract of the adrenal cortex, in conjunction with epinephrine given orally, is an important adjunct in the treatment of asthma. A summary of fifty cases of refractory asthma treated over a period of one year or more showed improvement in their allergic symptomatology in 84 per cent. Physical improvement in the same group was noted in 90 per cent. . . . Six of the thirty-five boys in this group presented nondescent of one or both testes, all six of which showed descent under treatment.—F. M. Pottenger, Jr., et al., California and West. Med., Oct., 1938, xlix, 271.

Burns.—On the basis of animal experiments, the author concludes that in severe burns, death is not due to toxemia due to disintegration of albumin, but to severe adrenal cortex injury. In animals with experimental burns, treatment with adrenal cortex and vitamin C caused better healing and lengthening of life. Therefore, in burns, Einhauser recommends internal treatment with adrenal cortex extract plus vitamin C in medium doses.—Klin. Wchnschr., Jan. 22, 1938, xvii, 127.

Colds.—In case a patient taking adrenal extract regularly notices symptoms of a cold, we recommend that he double the dose of the cortical substances when the first signs of a cold appear. By this method colds are frequently aborted. . . . The results of treatment in these patients were that one patient showed no definite improvement; five had no colds after therapy was commenced; three reported lessening in intensity of colds; nine reported lessening in frequency of colds; and nine reported lessening both in intensity and in frequency.—F. M. Pottenger, Jr., Med. Rec., Feb. 16, 1938, cxlvii, 165.

Colds, Depletion.—There can be little doubt that the adrenals play a very important part in resistance; every one is familiar with the feeling of lassitude that follows a cold. This is largely due to adrenal depletion.—S. G. Tippett, Prescriber, Jan., 1938, xxxii, 2.

Cough.—Whole adrenal gland, given by mouth, has been used in the treatment of 1,700 cases of respiratory disorders associated with a disturbing cough, during a period of eight years, with a clinical improvement in from 70 to 90 per cent. of the cases. The group of cases included acute rhinopharyngitis, acute bronchitis, chronic rhinopharyngitis, chronic bronchitis, whooping cough, and measles.—O. E. Barbour, Clin. Med. and Surg., Nov., 1938, xlv, 519.

Dyspepsia. Atonic.—There often is clinical evidence of atonic dyspepsia with coprostasis. It is accompanied by low blood-pressure and very pronounced asthenia. . . . The usual digestive medicaments ordinarily have little efficacy in this condition. On the contrary, it is modified rapidly and in a very remarkable way by the use of adrenal therapy.—J. Carles, Progres med., Oct. 18, 1919, xxxiv, 413.

Early Addison's Disease.—Patients with early Addison's disease may respond so well to therapy that under continued treatment they return to normal activity. They cannot be warned too emphatically that all stresses should be avoided. The false sense of security which is experienced may lead them to be careless, even going so far as to discontinue treatment.—Frank A. Hartman et al., Endocrinology, July, 1937, xxi, 516.

Graves' Disease.—. . . so far have found only one that has any notable effect, namely, the suprarenal cortex. . . . In over 50 cases we have found that feeding a glycerol emulsion of very fresh ox suprarenal cortex (glands from which 90 per cent of medulla has been removed) causes a striking gain in body weight and in muscle strength. These effects quite constantly begin to appear after two weeks of feeding.—David Marine, Am. Jour. Med. Sc., Dec., 1930, clxxx, 767.

Hypotension.—To give concretely the situation determined by this inadequacy [adrenal insufficiency] is to realize the import of the physiological activity of the adrenals. There is not a proper maintenance of tone of smooth muscle fiber and hence rapid changes in blood pressure take place with a predominant low systolic reading.—Walter Timme (Book, see Appendix) page 56.

Hypotension.—A diagnosis of hypo-adrenia was then made and the patients were given desiccated whole adrenal substance. This produced aggravation of a type which indicated that these patients were receiving an excess of adrenalin. Desiccated cortical substance was substituted with favorable results. Their symptoms were gradually alleviated, with a slow rise in blood pressure to normal. Mental tranquility was restored and later electrocardiograms showed normal heart action in all instances.—Fred Romer Reed, Am. Jour. Surg., June, 1938, xl, 514.

Infections.—The adrenal cortex is a part of the antibacterial defense mechanism, and is especially active in connection with the defense reactions against infection. . . . Adrenal support is in order as early as possible in all adrenal-stressing infections.—Henry R. Harrower, Clin. Med. and Surg., April, 1935, xlii, 178.

Infectious Diseases (Enteric).—Fifteen cases of enteric fever (7 typhoid, 8 paratyphoid) have been treated by intravenous injections of suprarenal cortex extract and vitamin C. In all but one case immediate improvement followed without untoward reactions.—Najib-Farah, Lancet, April 2, 1938, ccxxxiv, 777.

Infectious Diseases.—After influenzal attacks, for example, there is evidence that focal necroses occur in the adrenal cortex, with definite lowering of its endocrine function. The use of cortical extract in these cases seems therefore to be logical. Most other severe acute infectious diseases cause

similar changes in the cortex. Lowered resistance to infections is definitely raised by cortical extracts.—William Wolf (Book, see Appendix) page 986.

Infectious Diseases, Depletion.—The possible relation of the marked prostration following an attack of influenza to suprarenal insufficiency has been the subject of considerable discussion. Autopsy records appear to indicate that lesions in the glands are present in a large proportion of the fatal cases.—B. A. Cohoe, "Endocrinology and Metabolism," 1922, Vol. II, page 321.

Infectious Diseases, Toxic Syndrome.—Dr. Robert Clement and his co-workers reported a case in which the syndrome [malignant—symptoms of nervous origin such as adynamia, hyperthermia, cardiovascular and respiratory disturbance, digestive and renal symptoms, hemorrhages, and erythema] appeared on the fortieth day of diphtheria. After epinephrine, total epinephrine extract, ouabain and strychnine in large doses had been given, rapid improvement followed the injection of adrenal cortex extract.—Paris Letter, J.A.M.A., Jan. 7, 1939, cxii, 70.

Infectious Diseases, Convalescence.—The lowering of the blood pressure and the general apathy and indifference which so often characterises the period of convalescence may legitimately be traced to adrenal exhaustion.—I. Geikie Cobb (Book, see Appendix) page 91.

Neurasthenia.—Neurasthenia is a structure of the imagination, highly embellished with additions that have been made from time to time by many individuals, until it has become a huge edifice of which the characteristic features are weakness, lack of endurance of mind and muscle, and all the possible results of that weakness in its effects on internal organs. . . . Hypoadrenia may result from the wasting of old age, the toxins of the infectious diseases . . .or perhaps from exhaustion by long standing emotions. So that neurasthenia, we may realize, is hypoadrenia.—T. A. Williams, Am. Med., Aug., 1917, xxiii, 582.

Neurasthenia.—More and more attention is being paid to the relation between neurasthenia and the adrenal secretion. This disorder is often attributed to prolonged mental strain, and sometimes to physical causes (of which toxaemia is the commonest), although it is clear that either cause might produce an adrenal insufficiency.—I. Geikie Cobb (Book, see Appendix) page 91.

Tuberculosis.—On the physical side adrenal competency in childhood is one of our greatest protections against tuberculosis. In chronic tubercular disease hypoadrenia is nearly always present, and we rather neglect it. In chronic phthisis the blood-pressure is generally very low, and adrenal extract should form the basis of all treatment. It is the best of all tonics, and increases their powers of resistance to all microbic attacks. As the pressure rises the fever falls.—Thomas Bodley Scott, "Endocrine Therapeutics," 1922, page 39.

Vasomotor Instability, Hypotension.—It has been suggested that there are minor degrees of hypoadrenalism, characterised by lack of vascular tone, vasomotor instability, and low blood pressure. This is possible, since we can realise the strain which is thrown on the sympathetic-adrenalin apparatus in responding to prolonged mental and physical strain or to infections.—W. Langdon-Brown, "The Endocrines in General Medicine," 1927, page 74.

Vasomotor Instability.—. . . These patients have dizziness, light headedness, head pressure, with occasional digiti mortui. With these vasomotor disturbances we usually have a suprarenal deficiency [hypoadrenia], and it is accompanied by a condition which renders the patient subject to shock on slight provocation. We not only have clinical evidence of such disturbance,

. . . but we also have laboratory findings to support the diagnosis.—Walter Timme, New York Med. Jour., Feb. 7, 1920, cxi, 228.

Vomiting of Pregnancy.—After a thorough clinical trial over a period of two years, adrenal cortex therapy for the vomiting of pregnancy appears to be specific treatment if applied early in the course of the untoward symptoms. It has been found that the albuminuria of the later trimesters of pregnancy usually clears up when adrenal cortex therapy is instituted. This indicates that the presence of albuminuria also is evidence of a functional renal defect the result of a relative corticoadrenal insufficiency. In my opinion time and further clinical experimentation will demonstrate that eclampsia, in part at least, is also the result of a temporary relative corticoadrenal insufficiency of the last trimester.—W. N. Kemp, Med. Rec., Sept. 5, 1934, cxl, 239.

HARROWER ADRENAL PRODUCTS

Adrenal Cortex

ADRENO-CORTIN—CORTINORAL

Standardized Cortico-Adrenal Extracts

Indications: Addison's Disease; Subclinical Addisonism (Hypoadrenia); Asthenic and Cachectic States; Convalescence after Infections; Toxemia after Burns; Nausea and Vomiting of Pregnancy, etc.

Forms Available: (List Nos. 130A, 130S) **Sol. Adreno-Cortin**—each cc. contains the active, water-soluble, epinephrine-free extract from 40 Gm. fresh adrenal cortex. (Packages of five 1-cc. amp.; also in vials of 10 cc.)

(No. 131) **Cortinoral**—each soluble elastic capsule contains the active lipid fraction, representing ½ rat unit (Grollman). (Bottles of 50 and 250.)

(No. 129) **Adreno-Cortin Capsules**—each 5-gr. capsule contains a defatted desiccation of 30 gr. of fresh cortex tissue. (Bottles of 40.)

Standardization: Sol. Adreno-Cortin is biologically standardized to contain 2.5 rat units per cc. as determined by the Grollman method. (One rat unit is equivalent to approximately 22 dog units.) It is substantially free from epinephrine. Each capsule of Cortinoral represents ½ rat unit (Grollman). When fed to adrenalectomized rats, Cortinoral maintains life and normal growth. (See Appendix, page 116)

Dose and Administration: Oral: 1 cap. q.i.d., at or near meals. Parenteral: From 1 to 5 cc., or even more, daily, by intramuscular injection. Both forms may be given simultaneously. Salt (NaCl), half a teaspoonful in a glass of water t.i.d., ½ hour a.c., added to adrenal cortex therapy improves the prospect of benefit in sub-Addisonian adrenal insufficiencies.

Adrenal Medulla

ENDOPHRIN

Standardized Natural Epinephrine Solutions

Indications: Congested Mucosa as in Rhinitis, Laryngitis, Conjunctivitis, etc.; Superficial Hemorrhage (as topical application); Anaphylaxis; Urticaria; Shock; Asthma; etc.

Forms Available: (List No. 132) **Endophrin Solution** (1:1,000) in isotonic saline preserved with chlorobutanol 0.5%. (Bottles of 1 oz. for topical use.)

(No. 132A) **Sol. Endophrin** (1:1,000) in ampuls of 1 cc. for injection. (Packages of 100.)

(No. 164) **Endophrin Inhalant**—epinephrine hydrochloride 1% in isotonic vehicle with chlorobutanol 0.5% for oral inhalation. (Bottles of 8 cc.)

Dose and Administration: Topical (1:1,000, from bottle): From 2 to 10 min. locally. Parenteral (1:1,000, from amp.): From 3 to 15 min. p.r.n. Inhalation (1% sol.): From 5 to 10 min. is placed in an all-glass nebulizer (Endophrinizer), the nozzle is then inserted well into the mouth and, as the bulb is squeezed, the patient inhales deeply three or four times.

Note: No. 165, **Endophrinizer Outfit** contains one all-glass nebulizer with rubber bulb, one 8-cc. bottle of Inhalant in a convenient black leather, zipper case.

Pluriglandular Adrenal Formulas

ADREMIN (Adreno-Spermin)
Pluriglandular Tonic Therapy in Asthenic States

Indications: Post-Infectious Toxemias; Fatigue Syndrome; Asthenia with Suboxidation, Subnormal Temperature; Depletion Neuroses; etc.

Forms Available: (List No. 1) **Adremin Tablets** (or Capsules)—each 5 gr. contains Adrenal Substance (N.F. VI) gr. 1; Endothyrin gr. 1/12; Orchic Substance gr. 2; Calcisalin (excipient—see page 112) q.s. (Bottles of 100.)

(Nos. 1A, 1S) **Adremin Solution**—each cc. contains the water-soluble active material from 20 gr. fresh glands in the proportions: Adrenal (total) 3, Thyroid 3, Orchic 24. (Packages of five or 100 1-cc. amp.; also bulk vials of 10 cc.)

(No. 1D) **Adremin Drops** (Glycerite)—each cc. contains the glycerin-soluble ingredients from 99 gr. fresh glands in the proportions: Adrenal (total) 18, Thyroid 9, Orchic 72. For dosage purposes, 16 min. equals 3 tablets. (Dropper bottles of 25 cc.)

Dose and Administration: Oral: 1 tab. (or cap.) q.i.d. at meals and at bedtime. Continue for weeks. Desirable to double this dose for short periods. Drops: from 5 to 15 min. on tongue or in some convenient liquid (not hot) three or more times a day. Note: A series of injections may be combined with the oral therapy. Parenteral: 1 or 2 cc. subcutaneously or intramuscularly, daily or less often, preferably in conjunction with above. (Prohibit tea, coffee, strychnine, or other thyro-adrenal stimulants.)

Contraindications: Hyperthyroidism, Hypertension.

CORRELIN
Prophylactic Endocrine Support in Toxemias, etc.

Indications: Anticipated Depletion such as accompanies Acute Toxemias and Febrile Disease, especially in children.

Form Available: (List No. 100D) **Correlin Drops,** a glycerinated extract of the cortico-adrenal hormone combined with an extract of the spleen and gonads. Each cc. represents the soluble active principles from 46.2 gr. of fresh glands in the following proportions: Adrenal, Spleen, Orchic $\overline{aa}$ 15.4 gr. (Dropper bottles of 25 cc.)

Dose and Administration: Oral: 10 min. or more dropped on the tongue q.i.d. In acute fevers, 15 min. every two hours to effect. Parenteral: For supplementary therapy, inject from 2 to 5 cc. **Sol. Adreno-Cortin** daily or more often.

MENOCRIN FORTIOR (Adreno-Ovarian Co.)
Adrenal-Ovarian Endocrine Regulation

Indications: Menstrual and Menopausal Disorders associated with Asthenia, Hypotension, and Depletion. (See page 74.)

III.—THYROID THERAPY

"KEYSTONE of the endocrine arch" is a figure that has been aptly applied to the thyroid gland. For many years the thyroid occupied this key position in the government of glands undisputed, but the pituitary has effectively challenged its supremacy. Nevertheless, among the high command that subtly integrates the functions of the organs that make up the human machine, the thyroid ranks not less than second. Growth, metabolism, mentality, sexuality, and emotional stability are regulated in a large degree by this multipotent endocrine gland.

At a meeting of the Northumberland and Durham Medical Society, in 1890, Murray exhibited a patient with myxedema on whom he proposed to try thyroid therapy. His suggestion "was received with a douche of cold water," and one senior man present declared that he might as well expect an emulsion of spinal cord to cure tabes. But this time vision conquered incredulity.

Following the work of Baumann,[1] Hunt,[2] Marine,[3] and scores of others, thyroid therapy today rests on a well-established foundation, even though there are many parts of this complex problem that are still imperfectly understood.

Thyroxin

A TURNING-POINT in our iodine-thyroid knowledge occurred when Kendall[4] at the Mayo Clinic, on December 25, 1914, isolated an active thyroid derivative in crystalline form which he later named thyroxin. This was synthesized from phenol derivatives by Harington and Barger[5] in 1927. Since this substance, given intravenously, is capable of causing uniform increases in the basal metabolic rate (1 mg. increases the B.M.R. of the adult 3 per cent.), it was thought at first that these discoveries would lead to the complete abandonment of the cruder thyroid desiccations and their replacement with thyroxin. For a time its use did become fashionable, but the position now is entirely reversed. In 1924 Plummer and Boothby[6] of the Mayo Clinic stated that, for oral administration, they preferred desiccated thyroid standardized by its iodine content. Again, Reid Hunt[7] found that

". . . animal experiments show that thyroxin is in some of its effects less active, even by intravenous injection, than thyroid administered by mouth, the drugs being given in doses containing equal amounts of iodine."

Still more recently Gardiner-Hill[8] stated:

"Synthetic thyroxine, which has recently been introduced, appears to possess no advantages over the dried gland preparations—in fact, the majority of clinicians would probably agree that it is of distinctly less value."

So it is that "crude" desiccated thyroid has come back to replace its more refined descendant. This cycle has been repeated a number of times in the history of endocrinology, and the recalling of it should save us from the possible error of discarding a tried and true endocrine product in favor of a more

highly purified fraction from which essential elements may have been discarded. Thyroxin is not identical with thyroid secretion; adrenalin is not the only, nor even the most important, adrenal hormone, as we have already seen (Chapter II); and the reader will soon see (Chapter IV) that insulin is not the only contribution of the pancreas. This is not to deny the efficacy and importance of many of the highly concentrated active principles, but to emphasize that it is unwarranted and premature to consider their discovery as a mandate to abolish the cruder glandular desiccations.

There are many clinical indications that both these types of products have their place but, as happened in the case of thyroxin, we may yet find that some of the synthetic principles are not so useful therapeutically as their cruder but more complete antecedents. Incidentally, this is illustrated again in recent reports favorably comparing cruder liver extracts with the much more potent and specific antianemia fraction (Chapter V).

The Importance of Minor Hypothyroidism

THE history of thyroid therapy illustrates again a fallacy that has recurred too often in the development of organotherapy—the tendency to look for advanced conditions (cretinism and myxedema) as the sole indications for thyroid, rather than for the earlier signs of these lesions at a time when gross damage may be prevented. Undoubtedly this tendency is assisted by the preference of the writers of text-books and many scientific teachers for endocrinopathies that are rare and picturesque rather than for those that are common and more curable. Good teaching material may not be good "treating" material.

Etiologically, the thyroid is involved more frequently than any other endocrine gland, and thyroid therapy is of marked benefit in all conditions characterized by hypothyroidism. In fact, a beneficial response to such treatment is usually considered to be the best confirmation of a diagnosis of latent hypothyroidism. In hyperthyroidism, on the other hand, thyroid therapy is contraindicated. In such circumstances attention should be given to antagonizing factors that overstimulate the thyroid function. (See page 41.)

"Incipient hypothyroidism" is a term applied to an important condition that is by no means well recognized. Yet, as Hartsock[9] points out:

"Incipient hypothyroidism is by far the most prevalent and most difficult to recognize of all the types. If one keeps a mental picture of myxedema before him as a guide to the diagnosis of hypothyroidism, he will entirely overlook 75 per cent. of the patients who have very mild symptoms of great variation but who require specific thyroid substance for the relief of these symptoms."

As a matter of fact, one of the reasons for the wide application of thyroid therapy is now credited to its influence upon a condition known as cellular infiltration. It happens that this was one of the earliest findings, as the derivation of the term "myxedema" indicates. The appreciation of the broader implications of this fundamental principle elucidates not only the potentiali-

ties of thyroid therapy, but the endocrine etiology of many of the more remote disorders.

An explanation of this is taken from one of the writer's earlier books:[10]

"The principal hormone service of the thyroid gland has to do with the regulation of the intracellular chemistry. The exchanges in the cell evidently are dependent upon the catalytic influence of the thyroid principles, for when these substances are no longer supplied in proper amount there ensues a cellular inactivity (manifested by the reduced basal metabolic rate) that causes overloading of the tissues with their own half-destroyed waste products. The physics of this coincidence is easily explained: The half-changed products remain in the cell and, in accordance with the fundamental law of osmosis, there has to be an adjustment of the specific gravity of the cellular fluids to equal that of the fluids surrounding the cell. Therefore, additional water is drawn into the cell, causing it to become swollen, boggy, and water-logged. This mechanical phenomenon is responsible for a great many of the symptoms as well as anatomical changes in hypothyroidism of various degrees. It occurs in practically every tissue in the body except those in which it is physically impossible—the bones, for instance."

In early hypothyroidism the hallmarks of myxedema may be absent—slow pulse and respiration; mental dullness; physical lethargy; bloated, expressionless face; coarse, scant hair on scalp and eyebrows; indurated subcutaneous tissues; cold, dry skin, etc. Instead of a total myxedema there may be a regional myxedematous infiltration occurring in separate organs or systems, which is much more difficult to recognize. Escamilla and coworkers[11] describe a condition characterized by ascites, cardiac, intestinal, and bladder atony, secondary anemia, menorrhagia and associated carotenemia, with few if any external signs of myxedema. Maranon[12] suggests the term "extracutaneous myxedema," and cites instances of involvement of the mucosa of the nose, pharynx, larynx, digestive canal from mouth to anus, of the vulva, vagina, heart, liver, kidneys, and even the nervous system. Tinnitus aurium, a common and in some forms a rather intractable complaint, is not infrequently due to this type of regional infiltration. In his recent, practical book, Wolf[13] says that this type of tinnitus is "due to edematous or myxedematous infiltration of the mucous membrane of the middle or inner ear."

Signs and Symptoms of Early Hypothyroidism

THE earliest clues to hypothyroidism are noted in the hair, nails, and skin. Dry hair and skin; brittle, thick, coarse nails; and premature graying or falling of the hair should awaken suspicion of hypothyroidism. In the skeletal and muscular systems there may be vague muscular aches and pains, and it is well known that the tendency toward degenerative arthritis is always increased by a low metabolic rate.

If incipient hypothyroidism affects the central nervous system, it may give rise to restlessness, nervousness, and insomnia, rather than to the somnolence and lethargy of myxedema. Frequently recurring, chronic headache is often present. Infiltration of the ocular system may produce fatigue of the eye muscles, from which may come a host of vague secondary symptoms such

as headache, dizziness, neuralgia, and particularly exophoria which occurs towards the end of the day. Edema of the membranes of the nose and throat is often present, and annoying sensations in the ear are frequently due to swelling of the membranes near the orifice of the eustachian tube. This type of tinnitus is liable to occur and disappear several times the same day, and is relieved by thyroid medication.

Cardiovascular involvement in myxedema is usually evidenced by bradycardia, but in incipient hypothyroidism the pulse rate may be actually increased. Low amplitude of the electrocardiographic tracing indicates myocardial weakness, which may be due to thyroid insufficiency alone. The increased cholesterol content of the blood seen in hypothyroidism may be a factor in the production of arteriosclerosis, and it is possible that the progress of arteriosclerotic developments may be arrested by suitable thyroid therapy.

An atonic colon with obstinate constipation is characteristic of both myxedema and cretinism. Incipient hypothyroidism, however, may give rise to all types of indigestion due essentially to infiltration of the tissues of the gastro-intestinal tract.

When the genito-urinary system is involved, errors in diagnosis may be made by mistaking this lesion for nephritis because of the albuminuria. Impotence and sterility in both male and female may be due to simple hypothyroidism. A striking example of this was reported by McCullagh[14] and is referred to again on page 99. The author concludes:

". . . it appears that in this case hypothyroidism caused impotence by the production of a secondary testicular deficiency."

Some women with histories of frequent abortions are able to carry pregnancy to full term when appropriate thyroid therapy is instituted. Hypothyroidism is exceptionally detrimental during pregnancy, for it conditions the fetus to "an endocrinopathic inheritance." (See also page 85.)

Involvement of the hematopoietic system is most frequently manifested by a mild hypochromic anemia. In spite of the quite characteristic pallor commonly seen, the anemia of hypothyroidism is frequently neglected or overlooked. Bomford[15] points out that many patients with idiopathic hypochromic anemia have an appearance not unlike that of myxedema.

General symptoms unrelated to the infiltration of separate organs or systems may occur as a result of the decreased cellular function and inadequate oxidation in thyroid insufficiency. The patient often may complain of intolerance to cold and have a subnormal temperature. Lack of thirst and hypohidrosis are suggestive. Obesity, which may be generalized, or localized to the pelvic and shoulder girth regions, is unfortunately thought of as an almost invariable accompaniment of inadequate thyroid function. As a matter of fact, endocrine obesity is so often a pluriglandular problem, involving both the thyroid and pituitary, that it cannot properly be considered under one or the other of these headings. It is given limited consideration in Chapter VIII. Paradoxical as it may seem, it has been pointed out[9] that the

thin individual who has tried many means of increasing his weight may begin to gain immediately after institution of proper treatment of the thyroid insufficiency.

Importance of Thyroid in Pluriglandular Syndromes and Therapy

THE influence of hypothyroidism on the rest of the glandular system is vital. There are many examples of so-called "secondary hypothyroidism" similar to that of the hypogonadism cited above. Hartsock [9] states:

"Great advances have been made in specific glandular substitution therapy but thyroid therapy still remains the most potent and specific. It is of great value in the treatment of pituitary, thyroid, and ovarian types of polyglandular disorders in conjunction with other indicated hormonal therapy."

Numerous similar references appear in current medical literature, some of which will be found at the end of this chapter. We are glad to see that the pluriglandular idea has almost reached the stage of being "accepted." The writer long has stood for this principle and during years of derision and faint praise has emphasized its importance in diagnosis and therapy. Our confidence in it is reflected in our pluriglandular products and particularly in the addition of small amounts of highly purified thyroid substance (Endothyrin) to several of our formulas. As already pointed out, thyroid is particularly valuable in the treatment of pituitary, thyroid, and ovarian types of pluriglandular disorders. Menocrin (pituitary, thyroid, and ovary) is highly effective background therapy for menstrual and menopausal disorders (Chapter VI), while Pediacrin (antepituitary, thyroid, and thymus) has been used for many years with clinical success in the treatment of backward children (Chapter VIII). The glands form a democracy in which each is a member one with the other. Just as one sinner is said to corrupt many saints, so one deficient gland sooner or later inevitably will affect the physiologic integrity of the others. This, indeed, is the fundamental rationale of pluriglandular therapy.

The addition of thyroid to other indicated endocrine therapy certainly improves the response to ovarian, pituitary, adrenal, and other forms of glandular medication. Hutton [16] evidently had this in mind when he wrote:

"Desiccated thyroid in amounts just short of that producing tremor, tachycardia, nervousness, or irritability adds to the efficacy of treatment of any glandular deficiency with the possible exception of Addison's disease and the eunuchoid individual."

A hint of this is found in the following excerpt from an editorial review[17] of the progress in endocrinology during 1937:

"More than one eminent endocrinologist has recently admitted that certain glandular preparations often act better when combined with thyroid."

It is for this reason that thyroid has been said to act as an endocrine condiment to "bring out the flavor" of other glandular products administered simultaneously.

The Therapeutic Action of Thyroid

UNQUESTIONABLY thyroid therapy represents an excellent illustration of substitutive, or replacement, organotherapy. However, there is little doubt that it also has definite pharmacodynamic effects. Then, too, many experiences indicate that it has a homostimulative effect, for in many cases judicious thyroid therapy seems to put the patient's own thyroid on a better plane of service.

The careful reader will find in the literature several suggestions that thyroid is used too indiscriminately, and that the intelligent physician must first assure himself that the patient has definite symptoms of hypothyroidism, particularly a low B.M.R., before prescribing thyroid to effect. But Means,[18] by inference, appears to qualify the validity of this contention thus:

"It is logical to make use of thyroid in order to obtain the benefit of one of its physiologic (or perhaps in this connection we may say pharmacodynamic) actions in cases other than those of true hypothyroidism. It is the use of thyroid as a drug in contrast to its use as specific substitution therapy in genuine myxedema. It may be used for its calorigenic, its diuretic, its diaphoretic, its laxative, or other of its actions, for its effect on the female genital tract. . . . In short, it is an agent with a great variety of uses."

The homostimulative action of thyroid might explain part of its drug action. At all events, it is manifestly more desirable to reestablish the normal thyroid function than merely to replace the material that it fails to deliver to the organism. There are numerous published observations of this homostimulative effect. For example, Crile[19] says:

". . . we became impressed with the power possessed by thyroid extract over the growth of the thyroid gland itself. . . . Here we apparently have a case in which the function of the entire organism, including the thyroid, was stepped up by the administration of thyroid extract."

Again, Wolf[20] states:

"Thyroid extract is usually successful in the treatment of these hypothyroid states. It apparently acts not as a substitute for the secretion of the individual's own thyroid, but as a stimulant to the glandular function."

The observation that thyroid feeding is a means of stimulating the individual's own thyroid led the writer some years ago to suggest a simple method of testing thyroid function. The test consists essentially of giving definite and increasing doses of thyroid extract (U.S.P.) in a uniform and routine manner while a careful record is made of the pulse, respiration, and other symptoms that may occur. More information about this test will be found in Section 6 of the Appendix, and explanations as well as the material and chart for this test will be sent to any interested physician. On pages 14 and 83 it will be seen that organotherapy frequently serves as a means of demonstrating the patient's capacity to respond to this form of treatment, thus disclosing information that may be useful in confirming a diagnosis.

An absolutely reliable test of thyroid function might help considerably in the recognition of latent hypothyroidism in its more deceptive forms. The

trouble is, as Goldberg[21] has pointed out, that increased basal metabolism does not always accompany hyperthyroidism and, while hyperthyroidism with normal basal metabolism is rare, genuine instances have been reported. Hypothyroid states, especially in their early stages, certainly may not show a lowered basal metabolic rate as the test is usually made; and, if the basal metabolism equipment is used, several estimations may be required for each patient. Other methods of greater reliability have been suggested, such as estimation of the serum cholesterol, measurement of the circulation time, determination of impedance angle, etc. (See Appendix, Section 6.) One of the methods in current use may be perfected to the point where it will replace all others. At present the Harrower Thyroid Function Test is a simple and useful diagnostic measure for clinicians who do not have access to the more complicated tests. It has helped many physicians to avoid confusing hypothyroid states with chronic nephritis, arthritis, myocarditis, idiopathic hypochromic anemia, neurasthenia, etc.

Endothyrin

DESPITE the accomplishments in the study of the active principle of the thyroid, already mentioned, we still do not know in what form the thyroid hormone is present in the thyroid gland, or whether it may be present simultaneously in more than one form. The researches of Means, Lerman, and Salter[22] gave rise to the conception that the thyroid hormone is present in the gland in the form of a "dual hormone" containing both thyroxin and diiodotyrosine. This latter principle alone is found to exert no influence on gaseous metabolism, and its activity is conditioned upon its being present in combination with thyroxin. It is stated[23] that these two hormones together in the form of thyroglobulin are calorigenically more active than either alone. Hence, a thyroglobulin containing all the iodine in a given quantity of raw glands would seem to be the most clinically useful form of thyroid extract.

However, various thyroglobulin extracts differ in activity. The problem of thyroglobulin and other thyroid extracts has been investigated by The Harrower Laboratory for many years, and in 1925 we perfected Endothyrin, a product that contained twice the iodine figure of the U.S.P. thyroid. Today Endothyrin is a still more highly purified thyroglobulin extract containing 0.6 per cent. iodine. Whereas 5 gr. of raw thyroid is required to make 1 gr. of U.S.P. thyroid, 15 gr. of raw thyroid is required to make 1 gr. of Endothyrin. What does the discarded 14 gr. of raw material represent? The answer is more complex than it might seem perhaps, but it is certain that the discarded material has no iodine value and little, if any, thyroid activity. It is demonstrated by tests to be mainly inert tissue, and apparently some of it is, or can be, toxic. This is suggested by the so-called "feeding-to-the-death" experiments in which Endothyrin, U.S.P. thyroid, and other similar products are fed in progressively larger amounts to several groups of animals of the same average individual size and weight. Animals that are fed U.S.P. thyroid show

toxic symptoms and die quite a while before the animals receiving Endothyrin—in fact, all of the latter may be saved. Clinically, many physicians find that patients who are unable to tolerate a sufficient dose of thyroid to keep the B.M.R. normal are able to take Endothyrin.

While thyroglobulin, as in Endothyrin, is a thyroid extract and is generally considered to be the hormone responsible for all thyroid activity, it is not the official U.S.P. extract which contains an average of 0.2 per cent. of organically combined iodine.

It is impossible to generalize the dosage of Endothyrin or any other thyroid product. Not only does the required dosage vary with the individual, but two patients with identical basal metabolic rates may require different amounts of the same thyroid product. It is always a good plan to begin with comparatively small doses (Endothyrin, gr. ½ b.i.d. in adults) and to increase the amount every few weeks until the patient's requirement is found. The physician should supervise the patient closely, at least until the maintenance dosage is determined.

According to Hartsock[9] the greatest handicap to the proper treatment of thyroid deficiency is the widespread fear of thyroid medication. Strangely enough, this fear is quite as prevalent among physicians as patients, although it seems to be diminishing. Since thyroid must be given for long periods, some clinicians prefer to give occasional rest periods of a month or more. The required dosage certainly may become less in time, possibly because of a greater activity of the patient's own gland, as already suggested in quotations from Crile, Wolf, and others. However, the treatment should not be discontinued suddenly, except at the rest periods, but it may be reduced gradually. There is often a marked seasonal variation in the dosage required, more being necessary in cold weather.

Some thyroid preparations are offered in enteric-coated tablets, though the reason for this is not clear. Enteric coating may have some advantage from the sales-advertising point of view, but most clinicians will agree with Hartsock,[9] who concludes:

"I do not think it makes much difference whether it is taken on a full or an empty stomach or whether it is given in enteric coated capsules."

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THYROID—CLINICAL EXCERPTS

Alopecia.—Alopecia is sometimes a consequence of a hypofunctioning thyroid. When such is the case, a remarkable restoration of hair can be produced by thyroid feeding.—H. Lisser, Internat. Clin., Dec., 1933, iv, 67.

Amenorrhea.—Clinically I have yet to see a case with well-marked hypothyroidism in which amenorrhoea was not a prominent symptom, and more important still, in which the administration of thyroid did not reestablish the flow in a remarkably short time, and often after all other measures had failed.—C. B. Molony, Jour. Ment. Sc., Jan., 1927, lxxiii, 64.

Arthritis.—There are many cases [of arthritis] reported of considerable improvement under thyroid or poly-endocrine medication.—R. McE. Schauffler, Bull. Jackson Co. Med. Soc., March 30, 1929, xxiii, 7.

Cataract.—In presenting this small series of cases, we are convinced that the thyroid gland preparation used improved the general health of the patient in most instances. Whether the improvement noted in vision, and the disappearance of the opacities are the result of the specific action of the thyroid substance administered or merely the result of improvement of the general condition, indirectly influencing the eye, we are unable to state.—Wm. J. Kerr et al., Endocrinology, March-April, 1926, x, 126.

Constipation.— . . . stubborn constipation is even more characteristic of inadequate thyroid function, both in children and in adults; and in the former and in women in the late forties and fifties (Brown, 1931) may be sufficiently intractable to warrant the term, obstipation. This atony of the bowel musculature responds very nicely to thyroid extract. This was emphasized many years ago by Leopold-Levi and Baron de Rothschild (1913) in a treatise on "Minor Thyroid Insufficiency and Its Treatment." And now that basal metabolic rate determinations for the adult, and bone-age roentgenograms for infants and young children, are available as valuable diagnostic aids more attention should be paid to suggestive hints of hypothyroidism in patients with severe constipation.—H. Lisser, Internat. Clin., Dec., 1933, iv, 67.

Cretinism.—In cretinism much depends on an early diagnosis and the institution of thyroid therapy at the earliest possible stage. The results of thyroid therapy on the growth defect in cretinism are most satisfactory, provided that treatment is begun early. Under these conditions the physical standards reached compare favourably with the normal. It is more difficult to

assess the possibilities of improvement in the mental sphere. . . . It is probably true to say that the improvement in mental development is seldom as great as in the physical sphere, although examples could be quoted in which standards above average have been attained. The defects in sex development can be corrected by thyroid therapy, and with successful treatment the changes of puberty will occur at the normal age or very shortly afterwards. In females the menstrual cycle can usually be satisfactorily established.—H. Gardiner-Hill, Brit. Med. Jour., Jan. 16, 1937, 132.

Cretinism.—Thyroid treatment if administered early and during the first year of life and continued in proper dosage for a prolonged period accomplishes spectacular results in a certain number of cases. If not instituted early, more or less maldevelopment, physical and mental, will result that becomes less amenable to corrective therapy as the child grows older.—G. Y. Gillespie, Jr., New Orleans Med. and Surg. Jour., Oct., 1929, lxxxii, 231.

Cryptorchidism.—The treatment of cryptorchidism in this series is based upon the assumption that it is a symptom in the majority of instances of a disturbed thyro-pituitary-gonad relationship and not a clinical entity. Three methods are used: 1. Oral administration of thyroid and anterior pituitary extracts in increasing dosage; 2. Oral administration of thyroid and anterior pituitary extracts and hypodermic injection of anterior pituitary extract; 3. Oral administration of thyroid and anterior pituitary extracts and hypodermic injection of anterior pituitary-like (pregnant urine) extract. . . . Complete descent of the testes was obtained in the three methods as follows: First, 33 per cent.; second, 50 per cent.; third, 57 per cent. . . . Hypogonadism, especially when associated with adiposogenital dystrophy and hypothyroidism, responds in the majority of instances to oral administration of thyroid and anterior pituitary extracts and hypodermic injections of anterior pituitary-like extract.—M. B. Gordon, New York State Jour. Med., Sept. 15, 1936, xxxvi, 1313.

Dermatoses.—The thyroid is helpful in the maintenance of proper functioning and structure of the skin. It plays a part in providing the skin with an adequate amount of water and fat, a proper blood flow, and normal activity in the sweat glands. If thyroid activity is below normal, the skin is cold, dry and thickly infiltrated with a large amount of gelatinous matter, giving it the familiar mucoid appearance and feel, and rendering it susceptible to all types of dermatoses, notably ichthyosis, eczema, and psoriasis.—William Wolf (Book, see Appendix) page 224.

Dermatoses. Eczema.—Certain skin lesions characterized by dryness, particularly senile eczemas, ichthyosis and scleroderma, sometimes are improved by thyroid. The benefit here probably depends on the increased moisture of the skin induced by thyroid and perhaps by acceleration of skin growth.—J. H. Means, J.A.M.A., July 6, 1935, cv, 24.

Dermatoses. Pruritus.—General pruritus which is not associated with dermatitis and is not caused by scabies or other parasites or by soap, rough undergarments, or too frequent bathing in hot water or which cannot be explained as due to diabetes, jaundice, leukemia, senility, or any other disease such as urticaria is probably due to hypothyroidism. We have seen several such cases and have obtained good results from the administration of thyroid extract.—G. W. Crile (Book, see Appendix) page 191.

Dysmenorrhea.—Functional dysmenorrhea, or painful menstruation without any demonstrable cause, is one of the most common complaints, especially in young virgins, and is a probable indication of hypo-ovarianism. . . . In this condition, as well as in functional amenorrhea, the primary difficulty seems not infrequently to be due to a lack of thyroid hormone, because both disturbances may sometimes be at least partially relieved by thyroid feeding

alone. . . . Countless clinical experiments, however, have proved that at least in the case of a deficient functionation in the thyroid or ovary, organotherapy is more or less specific.—J. Rogers, Am. Med., March, 1926, xxi, 179.

Hypothyroidism.—Mild degrees of subthyroidism not sufficiently marked to warrant a diagnosis of myxoedema are probably more common than is generally thought. One or more of the following symptoms may suggest such a condition: dry skin and hair, mental depression or dullness, forgetfulness, loss of energy, a tendency to chronic constipation, a predisposition to colds, and some vasomotor disturbances; a useful confirmatory sign is a thinning or loss of hair from the outer third of the eyebrow. Such signs will indicate the administration of small doses of thyroid, and the improvement in the general health of this class of patient under such treatment is often remarkable.—D. Murray Lyon, Brit. Med. Jour., Jan. 23, 1937, 179.

Menopause.—When the basal metabolic rate is low and the blood cholesterol high, thyroid extract in doses of ¼ to 1 grain three times a day before meals, at times advantageously combined with pituitary extract (anterior lobe) in doses of 2 to 5 grains, is indicated. This usually overcomes the hypothyroid symptoms and signs, the tendency to obesity, and especially the peculiar constricting headaches so frequently complained of by many of these patients [menopausal].—William Wolf (Book, see Appendix) page 569.

Menopause.—The value of thyroid gland substance is already recognized for tiding over the symptoms which follow the loss of the ovarian function, more especially in those cases . . . in which the patient puts on weight too fast.—W. E. Fothergill, Practitioner, July, 1925, cxv, 43.

Menorrhagia.—This hypothyroid menorrhagia may occur at any age between adolescence and the menopause, but more frequently at puberty or in the thirties and forties. McCarrison (1917), Bell (1921), Falta (1923), Verco (1925), Crotti (1926), Berkeley (1926), Kern (1928), Lisser (1928), Isbister (1928), Cooke (1931), Lisser and Anderson (1931), and Breckinridge (1932) have testified to the gratifying relief of excessive uterine bleeding by administration of thyroid extract, when this symptom has depended on thyroid inadequacy. Most certainly, when such simple therapy is available, the application of radium, roentgen radiation and, worst of all, hysterectomy, are truly lamentable, if not inexcusable.—H. Lisser, Internat. Clin., Dec., 1933, iv, 67.

Menstrual Disorders.—Desiccated thyroid was given by mouth to 74 women having various types of menstrual disorders, accompanied by low basal metabolic rates without myxedema. The average age of these patients was 26.9 years. The thyroid dosage ranged from 0.5 to 3 grains daily. Definite improvement in the menstrual flow was obtained in 72 per cent. of the cases in which there was amenorrhea, in 55 per cent. of the cases in which there was oligomenorrhea, and in 73 per cent. of the cases in which there was menorrhagia. Seventy-five per cent. of the entire group of women, whether they experienced improvement in the menstrual disturbance or not, reported improvement in their general health after elevation of the basal metabolic rate to within the average normal limits.—S. F. Haines and R. D. Mussey, J.A.M.A., Aug. 24, 1935, cv, 557.

Mental.—Being now convinced that the clinical picture [psychosis], if not altogether due to, was undoubtedly complicated by hypothyroidism, I decided to try her on small doses of thyroid—½ gr. of the dried gland three times a day. Hand-in-hand with a hastening-up of the metabolic processes there followed a most remarkable clearing up of the mind. Within a fortnight her personality had altered beyond recognition, and she made a rapid and uninterrupted recovery.—C. B. Molony, Jour. Ment. Sc., Jan., 1927, lxxiii, 64.

Myxedema.—The prognosis in adult myxoedema is good and the clinical results of thyroid treatment are most satisfactory. In the course of about six weeks it can be predicted that the myxoedematous changes will have entirely disappeared and the patient be restored to his or her former condition.—H. Gardiner-Hill, Brit. Med. Jour., Jan. 16, 1937, 132.

Myxedema.—In adult myxedema the indication is to give a sufficient daily ration of thyroid to keep the patient free from symptoms. It is best to use the minimum dose that will accomplish this purpose. Nothing is gained by raising the basal metabolic rate to standard if the patient is free from symptoms (as is usually the case) at a decidedly lower level.—J. H. Means, J.A.M.A., July 6, 1935, cv, 24.

Obesity.—Most obese patients tolerate desiccated thyroid. . . . The more the obesity is the result of hypothyroidism, the more spectacular will be the desired response or reduction of weight.—A. A. Werner (Book, see Appendix) page 576.

Obesity.—In these cases, the fat is more or less evenly distributed over the body, and in frank cases the doughy, non-pitting lifeless skin makes the picture clear. The skin is rough and dry and the hair coarse, with a tendency to drop out. Low blood pressure, high blood cholesterol, and profuse menstruation are characteristic. Coupled with the low basal metabolic rate, the retarded mentality and the lazy sluggish disposition, the symptoms make diagnosis easy.—William Wolf (Book, see Appendix) page 513.

Obesity.—Thyroid has been much used in the treatment of obesity, which may be caused by different factors in different individuals. Some obese patients are definitely subthyroid, showing some of the signs mentioned above and often having a characteristic "round moon" face; in these thyroid extract is obviously indicated. It is also given in cases with no signs of thyroid insufficiency, and in those in which there is disturbance of the other endocrine glands.—D. Murray Lyon, Brit. Med. Jour., Jan. 23, 1937, 179.

Pregnancy.—Another form of organotherapy is now becoming increasingly popular—namely, the administration of thyroid. The rationale is more obscure than that which defines the use of other hormones, but it is based on the fact that the body during pregnancy makes great demands on the thyroid . . . the presence of an optimum amount of thyroxine is important for the progress of normal pregnancy. Whatever the exact rationale may be, thyroid therapy is undoubtedly as good as, if not better than, the other forms of hormone treatment outlined above. It is less costly and can be given orally. The dose recommended is thyroid extract 1 grain each day throughout the duration of pregnancy.—T. N. A. Jeffcoate, Brit. Med. Jour., March 27, 1937, 674.

HARROWER THYROID PRODUCTS

ENDOTHYRIN

A Highly Purified Thyroglobulin Extract (Organic Iodine 0.6%)

Indications: Hypothyroidism; Cretinism; Myxedema; Thyroid Obesity, etc.

Form Available: (List No. 125) **Endothyrin Tablets**—each contains ½ gr. Endothyrin (thyroglobulin) assaying 0.6 % organic iodine. (U.S.P. Thyroid contains from 0.17 to 0.23% iodine.) (Bottles of 50, 100, and 1,000.)

Standardization: Endothyrin is standardized chemically by estimations of its iodine content (0.6%), and biologically by feeding tests on small animals by means of which comparisons of toxicity can be made. The relation of fresh material to finished product is 15:1 (U.S.P.—5:1).

Dose and Administration: Oral only: From ½ to 2 tab. from one to four times daily. Endothyrin, as all other thyroid products, is best given in gradually

increasing doses. When metabolism is normal, maintenance dosage should be continued. Individual requirements may have seasonal variations. Many prefer to give one daily dose in the morning.

Contraindications: Hyperthyroidism.

THYROID (Harrower)
Thyroideum (U.S.P.) with Calcisalin Excipient (Iodine 0.2%)

Indications: Hypothyroidism as outlined above.

Forms Available: Compressed tablets of ¼ gr. (List No. 8), ½ gr. (No. 9), and 1 gr. (No. 10). (Bottles of 100, 500, and 1,000 of each.)

Standardization: Thyroid U.S.P. is standardized by estimations of its iodine content. (See U.S.P. XI, p. 388.)

Dose and Administration: Oral only: From ¼ to 2 gr. p.r.n., varying widely with circumstances.

Contraindications: Hyperthyroidism.

THYROID FUNCTION TEST (Harrower)
A Method of Evaluating Thyroid Function

Form Available: Each vial contains 12 tablets, 4 each of U.S.P. Thyroid (not Endothyrin) ½ gr. (colored red), 1 gr. (white), and 2 gr. (blue).

Dose and Administration: One tab. q.i.d., increasing dosage (in the order of "red, white, and blue") daily for three days, with the pulse record made and recorded on the accompanying chart at stated times. (Full explanations suitable for patients with each package—sent gratis to interested physicians. Not on sale.)

Contraindications: Hyperthyroidism.

Pluriglandular Thyroid Formulas

THYRO-PANCREAN CO. w. OVARY
A Formula for Controlling Hypertension

Indications: Hypertension associated with Hypothyroidism and Defective Carbohydrate Metabolism (Hyperglycemia). This syndrome is frequently seen at the climacteric.

Form Available: (List No. 30) tablets—each 5 gr. contains Endothyrin gr. 1/12; Pancreas (total) gr. 2; Ovarian Substance (N.F. VI) gr. 2; Calcisalin (excipient) q.s. (Bottles of 100.)

Dose and Administration: Oral only: 1 or 2 tab. q.i.d. for several weeks.

ADREMIN (Adreno-Spermin)
Thyroid, Adrenal, Orchic

Indications: General Tonic Agent in Depletion Syndromes with Hypothyroidism and Hypoadrenia. (See page 23.)

MENOCRIN (Thyro-Ovarian Co.)
Thyroid, Ovary, Antepituitary

Indications: Menstrual and Menopausal Disorders. (See page 73.)

MENOCRIN FORTIOR (Adreno-Ovarian Co.)
Thyroid, Ovary, Pituitary, Adrenal Cortex

Indications: Dysovarism with Depletion Syndrome and Hypoadrenia. (See page 74.)

IV.—PANCREAS THERAPY

BECAUSE of the brilliance of the discovery of insulin and its overwhelming importance in the treatment of diabetes mellitus, the attention of some physicians has been diverted from other extremely useful pancreas products. There can be no doubt that some other substance or group of substances in the pancreas is just as essential to life as is insulin. Pancreatectomized animals lose weight and die, even when given adequate diet and insulin. On the other hand, as an editorial writer in the Journal of the American Medical Association[1] once put it:

"By adding a daily allowance of raw pancreas to the diet, reinforced by insulin after pancreatectomy, the animals have been kept in a perfect condition of nutrition. Hence, it is concluded that the presence of something derived from the pancreas, either its digestive ferments or some internal secretion besides insulin, is necessary for the maintenance of normal metabolism."

Since the use of insulin constitutes almost a specialty in itself and has been so completely described in the many excellent books on the subject, it is not discussed here.

Pancreas Therapy in Food Allergy

A POTENTIALLY important form of pancreas therapy is the use of an insulin-free total-pancreas extract in syndromes based on food allergy. Oelgoetz is responsible for much of the experimental and clinical work that has given rise to this new approach to the ever-baffling problem of allergy. He believes that the underlying mechanism of allergies of food origin is a pancreatic hypofunction, which can be measured in some degree by an estimation of the serum-enzyme concentration of the blood. If this factor is reduced, imperfectly split protein substances are permitted to enter the blood stream, where in their incompletely digested form they are responsible for tissue irritation that gives rise to the allergic syndrome. Several interesting papers have been contributed by Oelgoetz,[2] and in one of them he says:

"Enzymes which are functionally identical with the pancreatic enzymes, are found in the serum, urine, feces, and in extracts of every organ and tissue of the body, except the heart and brain. That all of these enzymes are pancreatic enzymes would seem to be indicated by the fact that their concentration can be influenced by the administration of an extract of whole pancreas. . . . The prompt manner in which an active extract of whole pancreas influences the blood and urinary enzyme level, would seem to indicate that the pancreatic enzymes are absorbed from the gastro-intestinal tract, and that the serum and urinary enzymes are, in fact, pancreatic enzymes."

Oelgoetz and others have published clinical results indicating that certain types of allergic headaches, migraine, chronic urticaria, some forms of asthma, etc. may respond remarkably to such therapy. Another quotation from Oelgoetz[2] stresses the value of oral pancreas products:

"Clinically, the administration by mouth, of an active extract of whole pancreas, has been found to be effective by the writers, and by a number of

other careful clinicians. . . . We believe we have shown that the serum enzymes are in fact, pancreatic enzymes. When given by mouth, the pancreatic enzymes are absorbed in the active state. . . . Pancreatic hypofunction is quickly corrected by the administration of an active extract of whole pancreas."

The Harrower product, Panocrin-A, is a total, insulin-free pancreas extract, which has been used by many clinicians with satisfactory results in numerous cases in the foregoing categories that had resisted standard methods of therapy. Ragland [8] comments on his experiences and includes the following unusual case report:

"E.D.R., age 63, on January 22, 1937, complained of slowness in starting the stream of urine. The prostate was enlarged and firmer than normal. The urine was clear, but contained an excess of indican. The B.S.E. was minus 3. Forty-five (45) grains (3.0 Gm.) of Holadin were given daily. On March 3, 1937, there was no improvement, and the patient went East on business, returning July 19, when the prostate seemed the same. At this time he complained that his eyes tired too easily. His oculist was consulted, but reported nothing but the usual refractive error. Other treatment was tried until August 6, with no improvement, when Panocrin-A was started, 60 grains (4.0 Gm.) a day. Six days later he came to report that the congestion in the prostate had been relieved in seventy-two hours; that he had no difficulty at all in urinating; and that his eyes were very much better. He asked if he might keep on taking the Panocrin tablets, and was told that he could and should take them for a year."

While some of the work forming the basis for this theory may be repeated and modified as time goes on, there can be no doubt that a short course of Panocrin-A promptly increases the concentration of pancreatic enzymes in the blood. This can be measured by one of several blood-serum-enzyme tests. Naturally the normalization of the B.S.E. index does not always dispel all allergic symptoms, but in many cases there is a marked degree of clinical improvement. Because a therapeutic trial is inexpensive, can have no detrimental side effects, and is not time-consuming, it is worth while in patients whose allergic symptoms are suspected of being due to sensitivity to digestible materials.

The standard procedure is to give from two to four 5-gr. tablets of Panocrin-A four times a day, after meals and at bedtime, for the first week or ten days. The dosage is then reduced as the B.S.E. test or other circumstances indicate, and the smaller dosage continued for several weeks after improvement is noted.

Pancreas Tissue Extract in Angiospastic Syndromes

A SISTER product to Panocrin-A is commonly known as "pancreatic tissue extract," but by the several investigators in this field has been variously named angioxyl, kallikrein, and padutin. The Harrower product is called Panocrin-C. This substance possesses definite pharmacodynamic vasodilating properties. While in some ways its physiologic behavior resembles that of a hormone, its true endocrine nature is not established.

The vasodilating action of Panocrin-C is best demonstrated by its ability to neutralize the sympathicotropic vasoconstricting action of epinephrine. In fact, the solution is standardized on the basis of this action, each cubic centimeter representing 20 epinephrine-neutralizing units. (See Appendix, Section 5.) Panocrin-C rarely gives rise to painful local reactions and is free from histamine and choline.

Nowhere is the effectiveness of Panocrin-C shown more conclusively than in the increased walking capacity that it confers on patients with intermittent claudication. This is a condition that has long defied the best therapeutic efforts; but Roth, Barker, and Brown [4] conclude that the pancreatic tissue extract used at the Mayo Clinic is

". . . the only substance now known which has had definite and striking effect on the symptoms of intermittent claudication."

Angina pectoris is another distressing and common syndrome that may be modified by this treatment. The pain of angina pectoris, like that of intermittent claudication, apparently is due to muscular ischemia. This extract is capable of bringing about a remarkable dilatation of the coronary vessels so that the ischemia is relieved with gratifying results. Wolffe and associates [5] obtained clinical relief with their extract in 56 per cent., partial relief in 30 per cent., and failure in only 14 per cent. of their cases. In studying the influence of various remedies on the coronary flow of the perfused rabbit heart, Elliot and Nuzum [6] made the following striking comparisons:

"Following the use of pancreatic extract there was an average increase of 30 per cent. of coronary flow, 24 per cent. following the use of the Frey hormone [German pancreas extract], 15 per cent. following the use of metaphyllin, 13 per cent. following the use of theocin, and 9 per cent. following the use of caffeine citrate."

Other reports show the value of pancreatic tissue extracts in Buerger's disease, Raynaud's disease, Hirschsprung's disease, and in arteriosclerotic gangrene. The action of the substance in stimulating the parasympathetics and overcoming sympathetic overstimulation is shown in the work of Craven and McCrea,[7] who treated two boys with Hirschsprung's disease and found that pancreatic extract "produced contraction of both large and small intestines and the clinical improvement was considerable."

The essentially relaxant effect of this remedy has led to its use in several genito-urinary syndromes with benefit in ureteral spasm, postcystoscopic colic, and as an aid in the treatment of impacted calculi.

Very recently Wolffe[8] has reported on the use of an enzyme-free pancreatic extract in the treatment of one hundred cases of gangrene. Complete healing was obtained in as many as 75 per cent. This extract seemed not only to produce an early arrest of pathologic processes but to stimulate repair more rapidly and more completely than any other conservative method. The usual procedure with Panocrin-C is to give 1 cc. (20 units) by subcutaneous or intramuscular injection once or twice daily. As much as 1 cc. every four hours may be given on occasion.

Panopsin in Fermentative Indigestion

ANOTHER pancreatic preparation is obtained from the acinous cells of the pancreas, which are a rich source of the three pancreatic digestive enzymes—amylopsin, trypsin, and steapsin.

Panopsin is one of the strongest amylotryptic products available. One tablet of this preparation is capable of liquefying over 1,300 grains of raw potato starch. Using the methods outlined in U.S.P. XI (pages 275 and 276) it is found that the amylopsin in Panopsin will digest 540 times its own weight of starch in as short a time as thirty minutes, whereas its trypsin content will digest ninety times its weight of dry casein in sixty minutes.

The fundamental importance of the starch-, protein-, and fat-splitting enzymes of the pancreas has been understood longer than any other pancreatic function. Long before the isolation of insulin, pancreas products were being used with clinical satisfaction to facilitate digestion and assimilation and thereby to improve nutrition, particularly in chronic wasting diseases such as pulmonary tuberculosis.[9, 10] While this therapy rests on a firm theoretical basis, its more general application in conditions of malnutrition and fermentative indigestion has been delayed by the lack of sound experimental confirmation. It was asserted for many years that the enzymes given by mouth are inactivated by the gastric juices, but this is now disproved by the work of Ivy and his coworkers,[11] who state:

"In experiments designed to ascertain the amount of active malt amylase given with a cereal meal that passes into the intestine before the acidity rises to the lethal point of the enzyme, the minimum figure of 42 and a maximum of approximately 100 % was obtained, the average being 51 %."

Because of the opposing opinions on this subject, it will be well to quote from several recent reports of research emphasizing the rationale of pancreas ferment products in the control of digestive disorders. Selle and Moody[12] studied the effect of pancreatin on the fat and protein metabolism of depancreatized dogs. The quantity of the feces was reduced from 30 to 60 per cent., the elimination time approached normal, and the nitrogen loss in the feces was reduced by 30 to 60 per cent. The loss of fat, however, was not checked by this therapy. In view of a widespread impression that pancreatic enzyme products have to be enteric coated in order to be effective, it is important to note these workers' conclusions:

"There appears to be no uniform significant difference between the action of coated and uncoated pancreatin on digestion of fat and protein."

While it is true that high concentrations of hydrochloric acid do inactivate amylopsin, there is evidence that when a product like Panopsin is given just before or with meals, a significant degree of intragastric starch digestion occurs before the acidity of the gastric contents rises to the point of inactivating the enzyme. This is due largely to the fact that a mixed meal buffers the stomach acid so that the acidity does not reach the level of inactivation. It must be remembered that, despite the intragastric digestion, a large percent-

age of the enzymes reach the duodenum without being inactivated. In a later report Ivy and his associates [13] stated that when malt amylase or even ptyalin

". . . is administered with a meal a considerable portion of it passes into the intestine before the pH of the gastric contents is lowered to the point of inactivation of the enzyme."

It would seem, therefore, that the giving of fairly generous doses of Panopain (from 2 to 6 tablets) just before meals, so that it can exert its maximum digestive effects in the stomach as well as in the intestine, rests on a sound experimental and clinical basis.

From this evidence it appears that the only possible use for an enteric coating might be to protect the starch-splitting enzyme which, of course, is intended to be active in the stomach. The foregoing quotation from Ivy's paper shows that this enzyme is rarely inactivated by gastric acidity, though there is some evidence that enteric-coated amylopsin is more effective in achylia gastrica in experimental animals. (Even here the difference was comparatively slight.) However, it may be open to question whether or not the results of experiments in animals with complete separation of the pancreas and duodenum and fed on a fixed diet are directly transferable to human patients with carbohydrate indigestion. Under experimental conditions of this kind it might be more feasible to devise an enteric coating that would disintegrate at just the right gastro-intestinal location. It is impossible, however, to make a coating that will anticipate all the variations in human gastro-intestinal reactions and motility. Unfortunately, it has been the experience of many clinicians that an enteric coating is often "too perfect," so that the remedy is delivered intact in the stools. Enteric-coated Panopsin is available on request to Glendale, although we are not convinced that this process adds to the effectiveness of the product. Certainly clinical experience has assured a large number of patients and physicians that Panopsin taken ten or fifteen minutes before meals, as mentioned above, is a highly effective gastric as well as intestinal digestive aid.

Sympathetic Sedation in Hyperthyroidism and Sympathicotonia

IN discussing Panocrin-C, its ability to neutralize sympathicotropic stimuli was described. Whether this action is responsible for the reported capacity of pancreas extracts to control the sympathicotonic symptoms and signs of thyrotoxicosis is not yet established. Nevertheless, for many years pancreas therapy has been used with benefit in hyperthyroidism. Macdonald [14] suggests another interesting theory of action:

"The problem of Graves's disease may be solved by this simple theory, that it is through pancreatic insufficiency that the necessary amount of iodine is not absorbed from the food, for the pancreas has to do with the breaking down of carbohydrates, fats, and proteins."

Macdonald has made several reports on the treatment of toxic goiter with a total-pancreas extract and makes an earnest plea for a more widespread

trial of this therapy in early cases as a means of preventing the always regrettable destructive surgery of the thyroid gland.

Many other investigators agree that the etiology of thyrotoxicosis and its rational treatment lie outside the thyroid. Bram [15] has urged for years that exophthalmic goiter is a disorder of constitutional etiology and that, at best, surgery or radiation can be only palliative. Marine [16] reports excellent results from feeding adrenal cortex and believes that "the cortex produces a substance which tends to regulate or control thyroid activity." Bram also finds that adrenal cortex brings relief from the tachycardia, the heightened basal metabolic rate, nervousness, and fatigability.

Adrenal cortex is included in the pluriglandular pancreas formula now called Sydocrin (formerly known as Pancreas Co.—Harrower), which was designed more than twenty years ago from recommendations first advanced by Crotti. It has been used with clinical satisfaction as an endocrine sympathetic sedative, particularly in hyperthyroidism. The insulin-free pancreas extract offered as Panocrin-A is the chief ingredient, and there is more evidence for the antagonism between the pancreas and the thyroid than for any other gland. The clinical conclusions of Macdonald [14] already have been cited.

Incidentally, experiments by Balo and his coworkers [17] have disclosed the interesting fact that pancreas extract is capable of protecting animals against the toxic effects of thyroxin. Rabbits were given subcutaneous doses of thyroxin. Those protected with pancreas survived thirty-four days after the injection, whereas control animals died after fourteen days (on the average). The protective substance was not insulin for, when the animals were given 10 units of insulin daily, they were not protected against thyroxin poisoning.

Sydocrin is given by mouth as a means of overcoming the sympathetic sensitiveness of hyperthyroidism, hyperhidrosis, and certain non-thyroid toxemias (as tuberculosis). This therapy supplements the use of Lugol's solution or other indicated measures. The usual dosage is 1 tablet four times a day for a week or more, the dose then being doubled for a longer or shorter period, or increased still further, then reduced again. The suggested variation in dosage facilitates the determination of the individual responsiveness.

Adjuvant Pancreas-Secretin Therapy in Diabetes Mellitus

FINALLY we come to the fourth of our pancreas preparations and the first of its kind to be offered by Harrower. It is an extract from the Langerhansian cells, which it is well known are found chiefly in the tail of the pancreas. Combined with an acid extract from the duodenum, it is known as Pan-Secretin. Its main service is as adjuvant therapy in diabetes mellitus. For a long time it has been known that experimentally depancreatized animals receiving insulin lose weight and die unless pancreas derivatives are given concurrently by mouth. Thus, other pancreatic factors besides insulin are necessary for adequate metabolism and nutrition.

Undoubtedly, also, the action of some of the pancreatic products available is attributable to exocrine rather than to endocrine substances that they contain. However, there is much evidence of a relationship between the digestive and endocrine functions of the pancreas. Obviously digestion and assimilation of food are vitally related to the patient's insulin requirements. Okada and his coworkers [18] have recently demonstrated that hypoglycemia and hyperglycemia acting through the vagal centers may affect both the external and the internal secretions of the pancreas. Babkin [19] emphasizes the connection between external and internal secretions of the pancreas and recalls the work of Jones and associates, who showed that in sixty-eight cases of diabetes approximately half showed a diminution of pancreatic digestive powers.

Whether or not this non-insulin material is endocrine or exocrine in nature, certain it is that some pancreatic factor besides insulin is vital for adequate metabolism and nutrition—as already mentioned at the beginning of this chapter.[1] No matter how careful the dietary schedule and insulin management, depancreatized animals cannot live unless the regimen also includes the giving of pancreas derivatives by mouth. It would seem rational to assume that, since pancreas feeding is so vital in experimental diabetes in animals, similar therapy would be a useful adjuvant to the diet-insulin regimen in clinical diabetes mellitus. The value of this therapy is confirmed by a number of clinical reports. A striking example is that by Grayzel and Radwin,[20] who used a specially prepared pancreatic extract in the treatment of three patients with juvenile diabetes mellitus and hepatomegaly. In all three cases the blood lipids became lower and the liver decreased in size until it was no longer palpable. These workers concluded that the liver enlargement was probably due to fatty infiltration and that the therapeutic agent in the pancreatic substance was a lipotropic substance.

It will be noted that Pan-Secretin is a combination of an extract made from the tail of the pancreas, and duodenal extract. Incidentally, it is somewhat strange that, although the duodenum was the source of the first-named hormone (secretin), it is practically the "forgotten gland" among the endocrines.

The effect of duodenal extracts on carbohydrate metabolism is carefully reviewed in the Lancet for July 6, 1935 (page 30). Macallum and coworkers [21] found that, while the effects of duodenal extract on normal or completely depancreatized dogs was negligible, partially depancreatized dogs were definitely benefited when the substance was injected or given by mouth. Duncan and associates [22] treated thirty diabetics with duodenal extract. The results were somewhat inconstant, but it was possible to show definite effects when insulin and the duodenal extract were given together some days, and then the insulin suddenly stopped. Even with discontinuance of insulin, there could be obtained a normal sugar-tolerance curve, persisting for some weeks.

Referring to Duncan's work, Sir W. Langdon-Brown,[23] in his latest book, calls attention to the "double mechanism" regulating carbohydrate metabolism, in the following paragraph:

"If the recent claims are substantiated, that the oral administration of a duodenal extract can keep the blood sugar of a diabetic normal after he has first been treated by insulin, not only will this double mechanism have been proved for the internal secretion of the pancreas but a therapeutic advance of importance will have been made."

Pan-Secretin is by no means a substitute for insulin in diabetes mellitus —no more than Sydocrin is a substitute for surgery in advanced exophthalmic goiter. However, in older patients with mild diabetes (probably of pituitary rather than pancreatic origin, according to the conclusions of Houssay [24]), Pan-Secretin with proper dietary regimen may be adequate in controlling the condition. In true pancreatic diabetes, Pan-Secretin is a useful adjuvant to insulin and diet. In these cases this formula improves digestion and general nutrition, and in many cases appears to reduce the amount of insulin needed.

The suggested dosage of Pan-Secretin is from 1 to 4 tablets, with food, three or four times a day. Start with generous dosage, say 2 q.i.d., and gradually increase and vary the dose with the blood- or urinary-sugar values.

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6. Elliot, A. H., and Nuzum, F. R.: Jour. Pharmacol. and Exper. Therap., Nov., 1931, xliii, 463.
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12. Selle, W. A., and Moody, I. W.: Jour. Nutrit., Jan., 1937, xiii, 15.
13. Ivy, A. C., et al.: Jour. Nutrit., Jan., 1937, xiii, 29.
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15. Bram, Israel: Med. Rec., July 18, 1934, cxl, 67.
16. Marine, David: Am. Jour. Med. Sc., Dec., 1930, clxxx, 767.
17. Balo, J., et al.: Arch. f. exper. Path. u. Pharmakol., 1932, clxv, 594.
18. Okada, S., et al.: Nagoya Jour. Med. Sc., Dec., 1933, vii, 91.
19. Babkin, B. P.: J.A.M.A., Nov. 23, 1935, cv, 1659.
20. Greyzel, H. G., and Radwin, L. S.: Am. Jour. Dis. Child., July, 1938, lvi, 22.
21. Macallum, A. B., et al.: Jour. Biol. Chem., June, 1931, xcii, xx.
22. Duncan, G. G., et al.: Am. Jour. Med. Sc., March, 1935, clxxxix, 403.
23. Langdon-Brown, Walter: The Integration of the Endocrine System, page 41. (See Appendix.)
24. Houssay, B. A.: Am. Jour. Med. Sc., May, 1937, cxciii, 581.

PANCREAS—CLINICAL EXCERPTS

Angina Pectoris.—In conclusion, it may be stated from the data at hand, that enzyme-free pancreatic extract finds its best sphere of usefulness in angina pectoris associated with arteriosclerotic cardiovascular disease, with

or without hypertension, and that the other forms of angina pectoris require a more careful study as to the etiology of each case followed by indicated treatment.—V. A. Digilio et al., Med. Rec., Sept. 15, 1937, cxlvi, 245.

Angina Pectoris, Intermittent Claudication.—It is probable that the active principle of the pancreatic extract and the Frey hormone are identical, and that these preparations do not contain histamine, choline, adenylic acid, or adenosine, in sufficient quantities to explain their physiologic activity. The increase in the coronary flow and the antagonism to the pressor effect of adrenalin may explain the salutary influence of extract of pancreas as seen in the treatment of angina pectoris and intermittent claudication.—A. H. Elliot et al., Jour. Pharmacol. and Exper. Therap., Nov., 1931, xlui, 463.

Arteriosclerosis.—The arteriosclerotics, with or without hypertension and with abnormal electrocardiographic findings, varying from abnormal T waves to bundle branch block, were most likely to respond best to therapy with enzyme-free pancreatic extract. The age of the patient and the duration of symptoms did not appear to influence the outcome. It also seemed that associated diabetes and biliary disease did not modify the probability of a favorable outlook. There was no significant or sustained fall of the blood-pressure in the hypertensive group.—V. A. Digilio et al., Med. Rec., Sept. 15, 1937, cxlvi, 245; abstr., Clin. Excerpts, 1938, xii, 20.

Diabetes.—In animal experimentation, similar experiences have been noted. Fisher, Allan and others, Dragstedt and his coworkers, and others have observed that completely depancreatized dogs, even though they were treated with insulin, showed extensive fatty infiltration and degeneration of the liver. The changes did not occur, however, if the dietetic and insulin therapy was supplemented by the feeding of raw whole pancreas.—H. G. Grayzel et al., Am. Jour. Dis. Child., July, 1938, lvi, 22.

Diabetes Mellitus.—It would appear from experiments made by Laughton and Macallum (Can. Med. Assn. Jour., Sept., 1930, xxiii, 348) that a substance exists in normal duodenal mucosa which has a specific stimulating influence on the islets of Langerhans; in other words, an insular hormone. This, coupled with Workman's observations, introduces a new factor into the etiology of diabetes mellitus.—Abstr., J.A.M.A., Nov. 1, 1930, xcv, 1377.

Diabetes Mellitus.—It is possible that these pancreatic extracts given by the mouth may stimulate some internal secretion other than insulin which aids in the utilization of carbohydrates within the body.—C. B. S. Fuller, Brit. Med. Jour., May 12, 1928, 798.

Diabetes Mellitus.—Hill and Abram describe several cases in which the prolonged giving of secretin by the mouth eventually cleared up symptoms of severe cases of diabetes, which would suggest that secretin is not only necessary for the production of external secretion, but also stimulates the cell islands to produce the internal secretion.—W. M. Crofton (Book, see Appendix) page 80.

Gangrene.—Patients in my series of 100 cases of gangrene . . . seemed to do very well, presenting about 75 per cent. of complete healing. . . . Pancreatic extract (enzyme-free) proved of great value as an additional therapeutic agent in the management of diabetic and arteriosclerotic gangrene. It not only produces an early arrest of pathologic processes, but seems to stimulate repair more rapidly and more completely than any other conservative method in my experience.—J. B. Wolfe, Am. Jour. Surg., Jan., 1939, xliii, 109.

Graves' Disease, Diarrhea.—One certain fact is admitted by several of my colleagues—that the diarrhoea of Graves's disease is distinctly helped by the oral administration of pancreatic extract. In several instances parenteral

injections of vagotonine, a pancreatic hormone, have entirely stopped the looseness of the stools and even the goitrous symptoms have apparently improved. . . . In some instances the enlargement of the thyroid has disappeared, as also have the marked exophthalmos, tremors, and tachycardia; in fact, whatever the degree of the disease was, the patient always admits that an improvement set in after the oral administration of pancreatic extract.—C. Baird Macdonald, Brit. Med. Jour., June 4, 1938, 1231.

Hepatomegaly.—In three young diabetic patients with persistent hepatomegaly [associated with diabetes], striking recession of the liver to its normal size was demonstrated only after the addition of a specially prepared pancreatic extract. Adequate management of the diabetic condition with dietary control and insulin therapy alone had failed to accomplish this result.—H. G. Grayzel et al., Am. Jour. Dis. Child., July, 1938, lvi, 22.

Hypertension.—In eight of 108 patients suffering from hypertensive cardiovascular disease, a striking lowering in the systolic and diastolic blood-pressure was observed following the administration of tissue extract No. 568. Sixty-two per cent. of the treated patients obtained symptomatic relief which lasted for over a year. In the remaining patients treated with this extract, the effects on the blood-pressure were similar to those in the control group. In cases of essential hypertension a fairly constant, slight, temporary lowering of blood-pressure was observed which lasted only while tissue extract was being administered.—J. B. Wolffe et al., Jour. Lab. and Clin. Med., Jan., 1937, xxii, 374.

Intermittent Claudication.—The probable therapeutic value of the pancreatic tissue extract lies, first, in the fact that its use is perfectly safe and without disagreeable or toxic effects in the doses used, and, second, that it is the only substance now known which has had definite and striking effect on the symptoms of intermittent claudication. Its use for thrombo-angiitis obliterans and arteriosclerosis of the extremities probably will be restricted eventually to those cases in which this is the most prominent and distressing symptom.—Grace M. Roth et al., Proc. Staff Meetings of Mayo Clinic, Aug. 9, 1933, viii, 481.

Tuberculosis.—Pancreatic therapy is particularly indicated if it is desired to encourage an increase in weight in tuberculous patients who do not run a temperature. These individuals sometimes persist in being lean despite the improvement in their local condition. The results of the treatment are sometimes very remarkable. . . . Pancreas therapy in tuberculosis is in a way symptomatic treatment, of service particularly in patients who are improving as far as their local condition, but who still remain slender because the pancreatic assimilation is faulty. The dose recommended is ½ centigram a day in two powders with meals. The treatment is to be interrupted for five days each month. This treatment is harmless, but if no results are observed at the end of a month or a month and a half, it must be considered as useless. —L. Scheffler, L'Opotherapie clinique en vingt lecons, 1930, page 207.

HARROWER PANCREAS PRODUCTS

PANOCRIN-A

Insulin-Free Total Pancreas Extract

Indications: Pancreatic Insufficiency; Certain Food-Allergy Syndromes (Asthma, Migraine, Urticaria, Eczema, etc.) accompanied with low serum-enzyme values.

Form Available: (List No. 143) **Panocrin-A Tablets** (or Capsules)—each contains 5½ gr. (representing 30 gr. fresh) total pancreas. (Bottles of 100 and 500.)

Dose and Administration: Oral only: From 2 to 4 tab. q.i.d., after meals and at bedtime. Desirable to give heaviest dosage during first week, then reduce to 1 or 2 q.i.d. Continue for several weeks or longer.

PANOCRIN-C (Parenteral)
Pancreatic Tissue Extract ("Circulatory Hormone")

Indications: Angiospastic Syndromes; Intermittent Claudication; Angina Pectoris; Gangrene; Essential Hypertension.

Form Available: (List No. 143 S) **Sol. Panocrin-C**—each cc. contains 20 epinephrine-neutralizing units of the vasodilating pancreatic principle. (Vials of 10 cc.)

Standardization: Panocrin-C is standardized by its ability to neutralize the vasoconstricting sympathicotropic effects of given amounts of epinephrine. One unit of circulatory hormone is that amount which will neutralize the effect of 0.001 cc. of a 1:1,000 solution of epinephrine hydrochloride.

Dose and Administration: Parenteral only: 1 or 2 cc. daily or more often.

PANOPSIN
High Test Pancreatic Amylotrypsin

Indications: Digestive Disorders due to Pancreatic Deficiency; Indigestion; Adjuvant in Malnutrition, Sprue, Arthritis Deformans, etc.

Form Available: (List No. 23) **Panopsin Tablets**, coated—each 4 gr. contains 2½ gr. of a highly potent pancreatic digestive extract. (Bottles of 100 and 500.)

Standardization: One grain of Panopsin is capable of completely digesting over 500 gr. of raw starch in thirty minutes (method of U.S.P. XI, p. 275). Also in a separate test (U.S.P. XI, p. 276), each grain of Panopsin will digest ninety times its weight of dry casein in one hour.

Dose and Administration: Oral only: From 1 to 3 tab. 15 minutes before meals.

PAN-SECRETIN
Duodeno-Pancreas Therapy

Indications: Pancreatic Insufficiency; Carbohydrate Intolerance; Adjuvant in Diabetes Mellitus.

Form Available: (List No. 44) **Pan-Secretin Tablets** (or Capsules)—each 6 gr. contains Pancreas Extract (tail) gr. 3½; Secretin Extract (duodenal) gr. 1½; Excipient q.s. (Bottles of 100.)

Dose and Administration: Oral only: From 1 to 4 tab. (or cap.) with food three or four times a day. Start with large dosage, say 2 q i.d., increasing and varying amount according to blood- or urinary-sugar values.

SYDOCRIN (Pancreas Co.)
A Formula for Endocrine Sympathetic Sedation

Indications: Hyperthyroidism; Sympathetic Irritation; Hyperhidrosis.

Form Available: (List No. 6) **Sydocrin Tablets** (or Capsules)—each 6 gr. contains Pancreas Extract (insulin-free) gr. 3; Ovarian Residue (N.F. VI) gr. 1; Adrenal Cortex gr. ½; Total Pituitary (N.F. VI) gr. ½; Calcisalin (excipient) q.s. (Bottles of 100.)

Dose and Administration: Oral only: 1 tab. (or cap.) q.i.d., near meals and at bedtime. It is an advantage to increase this dosage occasionally to 6 or 8 tab. a day for two weeks, reverting to the standard dose and repeating. The essentially adrenal supportive (antiasthenic) effects may be increased by adding **Cortineral** (1 t.i.d.) or injections of **Sol. Adreno-Cortin**, 1 or 2 cc. daily or every other day. (See page 22.)

V.—LIVER THERAPY

DISCOVERY of the practically curative value of liver therapy in pernicious anemia turned an ominous and fatal malady into little more than an inconvenience. The Editor of the Lancet [1] exultantly called it "one of the most sensational episodes in the history of medicine."

In 1920 Whipple and his associates in the University of California found that, in dogs with secondary anemia resulting from repeated bleedings, it was possible to regenerate the blood-picture more rapidly and more satisfactorily under the influence of liver feeding. For five years the potentialities of this notion lay fallow, and it was not until 1926 that an announcement was made from Harvard University that Murphy and Minot had been successful in bringing about remissions in pernicious anemia by feeding calves' liver. In 1934 the Nobel Prize in medicine was awarded to Whipple, Minot, and Murphy for this work (the second of these prizes, by the way, given for epochal advances in endocrinology), and time will never dim the magnificence of their achievement.

In the early stages of the work, the idea that feeding liver could influence such a hopeless disease as pernicious anemia met with the customary derision and skepticism. We have already mentioned Sir Walter Langdon-Brown's amusing recollection of his own incredulity. When a friend wrote to him of the remarkable work being done in this country, he wrote back, "Wonderful men, these Americans; do they give bacon with their liver?" Fortunately, however, the effects of this particular therapy were dramatic and objectively measurable. The action of the oral administration of liver gave pause to some who were then saying that no gland product except thyroid was effective when given by mouth. The following from an article by Minot and Murphy [2] shows the type of the early reports:

"The study of 125 cases of pernicious anaemia treated with regularity for from three months to three and a half years with a diet rich in liver (180± Gm. daily) indicates that practically all patients with this disease are benefited, usually markedly and promptly. In almost all instances the red blood-cell count has risen above four million per cubic millimetre, and if the diet has been taken continuously and satisfactorily the counts have remained above this level to the present time."

It is not strange that the brilliance of the discovery of this fraction should have eclipsed to some degree the value of other liver derivatives. Nevertheless there are several other important liver products. In addition to Heparhemin, the pernicious anemia liver fraction, The Harrower Laboratory offers Anabolin, the so-called detoxicating hormone of the liver; Bilisalin, a highly purified preparation of the conjugated bile salts, included here because of its liver origin; Hematocrin, a combination of the secondary anemia liver fraction with iron and vitamin B; and Isocrine, a pluriglandular liver-spleen formula for use in certain functional hepatic defects.

Liver Fractions and Their Purification

SINCE Minot and Murphy's successful experiences, great strides have been made in the perfection of specific antianemia fractions. In this field also it seems that history is repeating itself. From a therapeutic point of view, commendable scientific zeal for breaking a substance down into several pure fractions sometimes succeeds almost too well. Frequently, of course, we really improve upon Nature, but at times she seems to rebuke us for our rude dissection of her gifts into their ultimate fragments. Just as an alkaloid does not always possess all the virtues of the plant from which it is obtained, so a highly purified fraction may not have all the advantages of the cruder material. In this connection, note the quotation from Harvier on page 11.

A report by Wills and Evans [3] from the London School of Tropical Medicine shows that in tropical macrocytic anemia crude liver extract is more effective than the antipernicious anemia fraction. They say:

"In conclusion it should be emphasised that at present all cases of tropical macrocytic anaemia, and those cases of sprue which show a macrocytic anaemia, should be treated with the cruder liver extracts and not with purified extracts alone."

Commenting on this, the Editor of the Lancet [4] remarks:

"The immediate clinical bearing of this work is noteworthy; if patients with macrocytic hyperchromic types of anaemia fail to respond to pure preparations of liver it is essential to try cruder preparations before deciding that they are resistant to liver therapy."

Very recently the work of Wilkinson [5] in the University of Manchester is mentioned in the Foreign Letters department of the Journal of the American Medical Association as follows:

"Thus it has been noted that the highly purified liver extracts may produce only reticulocytosis and partial or slow improvement in the red cells and hemoglobin percentage without the complete and rapid return to normal that follows the use of less highly purified liver extracts."

The U.S.P. Anti-Anemia Preparations Advisory Board uses the reticulocyte response in pernicious anemia patients as a measure of the potency of liver extracts, but they recognize the dangers of overpurification and do not accept too highly concentrated fractions.

Heparhemin: A Hemopoietic Liver Fraction

FOR the majority of cases of true Addisonian anemia, the antipernicious anemia fraction, sometimes called the "fraction G of Cohn," is a specific. The Harrower product is known as Heparhemin, each cubic centimeter of which represents the active antianemia substance obtained from 100 Gm. of fresh liver. Usually, 1 cc. daily is adequate for a maximum reticulocyte reaction, but the dosage must always be governed by the response of the patient. The only sound criteria of success are repeated hemoglobin and red-cell determinations, and it is good practice to maintain the hemoglobin above 100 per cent. and the red-cell count somewhat above normal. Patients who are in

relapse will need 1 or 2 cc. daily for a few days at least. For maintenance dosage, the average patient will not require more than 1 cc. weekly, and many patients remain hematologically and clinically "cured" on a dosage of 1 or 2 cc. a month.

In addition to its use in pernicious anemia, Heparhemin is frequently used as adjuvant therapy in a variety of conditions such as sprue, tapeworm infestation, pellagra, X-ray sickness, hyperemesis gravidarum, etc. Liver therapy apparently stimulates leukocytosis as well as reticulocytosis, and it has been shown by Wilson and Carey [6] that patients with pneumonia and a relatively low white count respond especially favorably to this type of leukopoietic treatment.

Compound Hematinic Therapy in the Secondary Anemias

POPE'S immortal words, "Be not the first by whom the new are tried, nor yet the last to lay the old aside," give sound therapeutic advice. Medicines may have fashion cycles. The forces of skepticism and belief are constantly at work and both have had their uses and abuses. Sometimes skepticism drives a useful substance out of therapeutics and there may be an interval of many years before its revival. One of the best modern examples of this is iron therapy in anemia. Used correctly by Blaud, Niemeyer, Immerman, Osler, and many other great clinicians of the last generation, it was largely discarded and thrown into disesteem. As Haden [7] states:

"The most recent development in iron therapy has been the renewed emphasis on the greater potency of ferrous salts. While any iron preparation is effective if given in large enough doses, very much less of the ferrous compounds needs to be taken. . . . These principles, forgotten by clinicians for many years, have only recently been learned anew. Such rediscoveries emphasize again our debt to the great clinicians of the past."

Haden points out that as late as 1925 results of experiments were published showing that inorganic iron is absorbed. At that time, however, authorities believed that the absorbed iron was not converted into hemoglobin and, therefore, that oral iron administration was valueless. Due to the researches of Witts and others, this assertion is now entirely refuted and the two fundamental principles of iron therapy are being re-emphasized: (1) Iron must be administered in large doses to be fully effective; and (2) the ferrous salts are preferable. The iron-hemoglobin conversion is probably facilitated by vitamin B. Witts [8] states:

"Pyrrole derivatives such as bile pigment, chlorophyll, and the cytochrome of yeast potentiate the action of iron, probably by facilitating its conversion into haemoglobin."

Liver has a place also in the treatment of the secondary or hypochromic type of anemia. In fact, Whipple's original experiment was performed on dogs with an experimentally produced or secondary anemia. The secondary anemia fraction of Whipple is very effective, particularly when used in combination with iron. Murphy [9] states:

"Liver, given in large doses as in the treatment of pernicious anemia, is also effective in secondary anemia. Combined with iron therapy, as described, the effect will be greater than if either measure is used alone."

This synergism between liver extract and iron has been referred to many times, particularly in the several secondary types of anemia. For instance, Dyke [10] says:

"In certain cases of secondary anaemia, liver therapy is effective in causing a reticulocyte response and in raising the blood-count. The best results are to be looked for in those cases of secondary anaemia due to failure of blood regeneration after haemorrhage. The effect of the liver therapy is greatly enhanced by the simultaneous exhibition of iron."

Another element essential to normal hematopoiesis is the vitamin B complex. As Dameshek [11] states:

"The vitamin B complex, whether or not it is identical with the extrinsic factor, is probably an essential element in normal hematopoiesis."

The combination of these three useful substances—the secondary anemia liver fraction, ferrous sulfate, and vitamin B concentrate—is offered by Harrower under the name Hematocrin. It is an effective agent in the secondary or iron-deficiency hypochromic anemias. The chief examples are the nutritional anemia due to deficiency of iron in the diet; hemorrhagic anemia due to menorrhagia, metrorrhagia, etc.; the anemias of pregnancy, surgical convalescence, chlorosis, etc. Hematocrin may be important supplementary therapy in patients whose treatment includes restricted diet, as in colitis, gastritis, peptic ulcer, and other gastro-intestinal disorders. There is evidence that quite a high percentage of people, particularly women in sedentary occupations, may show significant degrees of secondary anemia. Clinical reports indicate that when the blood-picture is restored to normal by the use of Hematocrin the general health is greatly improved. The usual dosage is 1 capsule q.i.d., p.c. This measure is continued for some weeks and may be supplemented with injections of Heparhemin or the cruder Liver Extract (Harrower), which is a definitely valuable product, despite the fact that its potency is one-tenth that of Heparhemin.

Anabolin in Functional Hypertension

IN 1924 two Canadian physicians, Macdonald [12] and James [13] showed that certain liver extracts were capable of reducing the blood-pressure. About the same time, Major [14] was working on a guanidine-neutralizing blood-pressure-reducing principle extracted from liver. In 1925 the research department of The Harrower Laboratory announced the standardization of a stable depressor liver extract which was believed to be the active principle previously described by Macdonald. Because its effects seemed to be brought about by intensifying the anabolic functions of the liver, it was named Anabolin. Apparently this substance is a true detoxicating hormone.

Some years after the introduction of Anabolin, workers at the Tohoku Imperial University at Sendai, Japan,[15] perfected a liver fraction named Yakriton, which they claimed to be the "detoxicating hormone of the liver."

Yakriton appears to be practically identical with Anabolin and has been shown to inhibit toxic symptoms of heavy doses of ammonium chloride, histamine, or even chloroform. It increases the capacity of the liver to detoxicate protein poisons, phosphorus, and phenol. The survival period of rabbits with artificially induced tuberculosis has been doubled by use of this preparation.[16]

Among the clinical reports, Flipse [17] showed that liver extract was a useful adjuvant in the treatment of hypertension, especially when the pressure is at a dangerous level. It was effective in many cases in which nitrites and related vasodilators failed to reduce the tension.

A more recent report by Willis [18] states:

"I have used for many years the Harrower product called Anabolin. One cc. given hypodermically will generally reduce a very high pressure 20 mm., which drop will be maintained for ten to twenty-four hours. It may be desirable to give a second 1 cc. at from six- to ten-hour intervals to bring about a pressure drop compatible with safety. Where this remedy is effective, and it oftentimes is spectacular in its effect, the rate of pressure drop slows as it approaches a high normal reading."

The action of Anabolin is clearly intrahepatic. It does not have a direct action on the arterioles such as is produced by the nitrites. It is entirely protein- and histamine-free, and apparently acts by increasing the capacity of the liver to destroy waste products, many of which are undoubtedly pressor substances.

Anabolin is standardized by its effects on the blood-pressure of normal animals. The standard solution contains 12 hypotensive units per cubic centimeter, whereas a double-strength product known as Anabolin Fortior contains 24 hypotensive units. The various endocrine units are defined in Section 5 of the Appendix.

Organic cardiovascular, renal, and intrahepatic damage obviously will limit the effectiveness of Anabolin. However, in patients without severe structural changes, especially when seen early in the course of hypertension, Anabolin often has a decided hypotensive effect which can be maintained with suitable continuance of the therapy. It has also been used in other conditions, such as diabetes, rheumatism, gout, allergy, and chronic malnutrition, in which it seems desirable to attempt to step up the hepatic detoxicating function.

The hypertension of late pregnancy and the serious disorders that may follow it, such as eclampsia, apparently are the result of a profound breakdown in detoxication. Although there is frequent evidence of renal involvement, the suggestion is that the liver may be the principal point of attack and that in many cases the kidneys are affected secondarily. Miller and Martinez [19] report on fifty cases of pregnancy toxemia, including seven of eclampsia, that were treated with liver extract with excellent results. More recently these same authors [20] report on 255 cases of pre-eclampsia with good, but not spectacular, effects.

The hepatic factor in such conditions as asthma has recently been stressed by De Bersaques and Berat,[21] who suggest the addition of the liver detoxicating hormone to the other treatment of these conditions.

Anabolin is obtainable in tablets as well as in solution, and the following dosage has proved satisfactory: In the morning, after taking the blood-pressure, inject 1 cc. of the standard solution intramuscularly. Take the blood-pressure again in the late afternoon and, depending upon developments, inject 1 cc. each day or every other day as seems advisable. Then give the tablets, 1 t.i.d., in conjunction with the injections and continue the oral therapy for quite some time. The indicated hygienic and dietetic measures should be followed throughout the treatment.

Isocrine in Chronic Liver Defects

ISOCRINE is a combination of Anabolin, hepatic substance, spleen extract, and boldine hydrochloride. (Boldine is a plant extractive that has a peculiarly marked influence on urea production.) This formula apparently enhances the functional capacity of the liver, particularly its ureagenetic function. Hence, one of its chief indications is defective hepatic physiology accompanied with a low urea index. It is given by mouth, usually 1 tablet q.i.d. Injections of Anabolin may be desirable at the beginning of treatment, which should be continued for not less than two months.

The Bile Salts in Therapy

BILE cannot properly be called a glandular extract, but it is an endocrine cousin. It originates in the liver, and the efficiency of this gland and of the pancreas depend to a large degree on the bile. Thus bile is a natural and effective adjuvant to many organotherapeutic measures. It is sometimes forgotten that in addition to all its well-known digestive, absorptive, antiputrefactive, and laxative functions, bile seems to possess another function which, although not yet perfectly understood, makes it essential to life. Biliary stimulation is valuable "foundation therapy," and, as Best and Taylor [22] state:

"The natural and the most powerful excitants of biliary secretion are the bile salts themselves."

The bile salts, sodium taurocholate and sodium glycocholate, occur in combination with many other substances in the complex fluid which is bile. By separating these bile salts from the undesirable ingredients and preparing them in a highly purified, concentrated form, The Harrower Laboratory has perfected Bilisalin.

The action of bile salts in stimulating biliary secretion might be called homostimulative or self-perpetuating. Regarding this, Brown and Dolkart [23] say:

". . . since the liver cells are directly stimulated to secrete, more bile passes through the biliary apparatus, probably because of improved mechanical flow resulting from the increased amount of bile from the liver itself."

Because gall-bladder bile contains a higher concentration of bile salts, which are absorbed more rapidly into the blood stream and carried back to stimulate the polygonal cells of the liver, it has been called "ignition bile." Bilisalin imitates quite closely the action of this ignition bile and acts as the most natural cholagogue to stimulate biliary secretion. Hence, it is a physiological remedy for hepatobiliary stasis and for the conditions underlying many types of chronic constipation.

Many of us are not aware of the frequency of hepatobiliary disorders. Crump [24] reports abnormal biliary findings in nearly 40 per cent. of a thousand adults coming to autopsy. Graham [25] has said that 40 per cent. of the adult population suffer from biliary tract disorders at some time in their lives. Treatment of these conditions has been left too much to the surgeons, a fact which they themselves are beginning to realize.[26] Much recent work stresses the importance of bile salts in the "non-surgical drainage" of the biliary tract as a preventive treatment of hepatobiliary disorders. It is well known that any factor that tends to impede the free movement of bile from liver to duodenum has serious consequences, not only at the point where the impediment occurs but upon the exocrine and endocrine functions of the liver, upon the digestive processes in the bowel, and upon the intestinal peristaltic activity. With purified bile salts it is possible to correct hepatobiliary stasis and in many cases to prevent its reaching surgical proportions.

The older bile salts preparations as powdered extract of ox-gall U.S.P. were objectionable because of their impurities, but Bilisalin is a natural conjugated bile salts product entirely free from bile pigments, mucin, and cholesterol; nor does it contain any cathartics. Other fractions of bile have been prepared, principally the crystalline dehydrocholic acid. As not infrequently happens, however, the enthusiasm for single-fraction chemical purity, commendable as it is, does not appear to be the best answer to the problem, although of course these acids have a valuable place. Recent research indicates the superiority of natural bile salts and acids over the unconjugated acids. For example, Doubilet [27] finds that

"Oral administration of large amounts of the various bile acids to dogs with a common duct fistula indicates that, from the point of view of largest excretion of bile acids in most concentrated form, the natural bile acids of the dog were probably the most efficient. Under the conditions of these experiments pure ox bile salts and glycocholic acid were found to be more efficient than the unconjugated cholic and desoxycholic acids. The natural bile acids (cholic and desoxycholic acids, and their various conjugated forms) were more effective than dehydrocholic acid."

This has been confirmed by Ivy and associates,[28] who report:

"The conjugated bile acid preparations . . . proved superior as stimulants to the flow of bile containing increased amounts of biliary constituents."

In addition to its importance in biliary insufficiency, intestinal stasis, duodenal indigestion, etc., Bilisalin seems to have an important place in the preoperative and postoperative treatment of cholesterol gall-stones. It has been

shown that adequate amounts of bile salts in the bile tend to keep cholesterol in solution. Further, Morrison and coworkers [29] showed that cholesterol gall-stones experimentally placed in the gall-bladders of animals were reduced in size by feeding large quantities of ox bile. Oral administration of pure bile salts not only helps to prevent formation of cholesterol stones by increasing the concentration of bile salts in the bile, but by its cholagogic effect the greater volume of bile tends to keep the bile passages flushed out. Precipitated solid matter, inspissated bile, nidi of infection, etc. are removed and thus absorption of toxic substances is reduced. For these reasons it has been said that suitable bile salts therapy acts as a "physiologic cholecystectomy." Certainly this therapy is rational in patients with cholecystitis or other conditions known to favor the formation of stones; and in patients who have had gall-bladder surgery, Bilisalin may be used as an adjuvant in the hope of preventing re-formation of stones.

Since patients with biliary tract disturbances are notoriously subject to constipation, this therapy has a double value because the increased production and free flow of bile act as a natural laxative. It has long been a Harrower principle to resist the common, but unphysiologic, practice of including one or more cathartic drugs in bile salts formulas. The correctness of this practice becomes apparent in view of all the recent work. If hepatobiliary stasis is the basis for constipation, then this underlying fault should be corrected. Artificial irritation of the bowel will not rectify it, but will merely obscure the issue from the patient. Bilisalin may be given in large amounts over long periods with no toxic effects; and, when given in the manner recommended, constipation is frequently corrected by overcoming the hepatobiliary stasis.

Since gall-stones are particularly common in obese women during the last few months of pregnancy, and since at this time there is often a high cholesterol level in the blood, such preventive therapy seems to be rational at this time. Bilisalin has also been used to improve the visualization in oral dye tests of gall-bladder function. Obviously, it should not be given in the presence of complete obstruction of the hepatic or common duct.

Another therapeutic potentiality of bile, which has not received much attention in this country, was proposed by Henri Roger [30] thirty years ago. He believed that the intestinal walls secrete a ferment called mucinase, which is capable of coagulating mucin, and that this ferment is rendered inactive by certain substances in the bile. He maintained that mucous colitis is frequently associated with biliary insufficiency and may be produced invariably by experimentally diverting the bile flow from the duodenum. Nepper [31] concludes that mucomembranous colitis is due to oligocholia and indeed cannot exist without it. Roger states:

"For those who pass membranes, prescribe an extract of ox-gall, and you will frequently see a subsidence of the pain and a complete disappearance of the membranous casts."

Whether this theory of the etiology of mucous colitis and Roger's description of the modus operandi of bile in the treatment of this lesion are correct or not, many clinicians have found that adequate bile salts therapy gives these patients a great deal of relief. Undoubtedly many of their toxic syndromes are attributable to hepatic torpor and biliary insufficiency, conditions in which Bilisalin is most excellent adjuvant treatment.

Bilisalin, formerly called Bile Salts Co. (Harrower), is an efficient cholagogue tablet containing 3½ gr. of highly purified bile salts with hepatic extract as the excipient. No laxatives are added because of their interference with proper dosage. It is an advantage to give it in a step-ladder fashion as follows: Prescribe 1 tablet four times a day between meals for two or three days, double this for three days, treble the dose for three days, continuing or not according to developments. The presence of free bile in the stools is an indication to reduce the dosage, so the patient should be told to watch for the yellowish-green bile floating upon the water in the toilet. When this appears, omit treatment for a few days; then commence again with the original dose and increase either at the former rate or with longer intervals. Continue this irregular procedure for several months.

As an adjuvant in chronic diseases and diatheses, as well as in all forms of hepato-alimentary torpor and toxemia, Bilisalin will be found of decided merit. It is superior to the various cathartic and liver-stimulating drugs, if only for the excellent reason that it is a natural, non-irritating, and non-habit-forming remedy.

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LIVER—CLINICAL EXCERPTS

Anemia, Hypochromic.—The secondary anemia liver fraction of Whipple and his coworkers [with iron and ammonium citrate] has been administered orally to 11 patients with chronic hypochromic microcytic anemia. A rise in circulating reticulocytes occurred in every case. Through the application of the principle of the double reticulocyte response to control the iron content of the liver fraction, it appears likely that the liver fraction contains reticulocytogenic material apart from its iron content.—W. H. Barker et al., Am. Jour. Med. Sc., March, 1938, cxcv, 287.

Anemia, Pernicious.—Treatment consists in the administration of one or more of the anti-anaemic factors present in stomach or liver, but they must be given in sufficiently large amount to maintain a normal blood picture and clinical condition—this can only succeed if therapeutically active preparations are used. . . . If there are any signs or symptoms, however slight, of involvement of the nervous system the treatment must be continued in full doses without relaxation. The prognosis in uncomplicated cases of pernicious anaemia is good provided that these points are borne in mind and that adequate treatment with an active preparation is taken for the rest of the patient's life.—J. F. Wilkinson, Practitioner, March, 1935, cxxxiv, 272.

Anemia, Pernicious.—From these four cases, we cannot conclude that all patients with pernicious anemia would be able to store the excess of massive doses of active principle given over a short period of time. . . . However, each of these patients shows evidence of storage of some of the active principle, which storage has enabled each one to maintain normal blood levels for a relatively long period of time.—F. R. Miller, Proc. Soc. Exper. Biol. and Med., Jan., 1936, xxxiii, 580.

Anemia, Pregnancy.—Anaemia of pregnancy is sometimes simply of secondary type, in which the greatest amount of benefit is derived from administration of iron. In some cases, however, an anaemia develops of the hyperchromic type closely resembling pernicious anaemia, and these cases are probably best treated by a combination of iron in large doses and liver extract in moderate amounts.—J. D. Comrie, Prescriber, Feb., 1935, xxix, 41.

Anemia, Secondary.—Treatment by means of intramuscular injections of solution of liver extract together with adequate doses of iron (ferric ammonium citrate) by mouth is the most effective, although the combination of large doses of whole liver and iron by mouth is very effective but less readily used.—W. P. Murphy, Arch. Int. Med., May, 1933, li, 656.

Anemia, Secondary.—Secondary anaemias following loss of blood or chronic diseases such as colitis, syphilis, malnutrition, etc., are of the hypochromic type. In addition to general regimen, such as good diet, they require

especially iron preparations and are in general benefited by some of the products containing vitamin B. Extract of liver or stomach in moderate doses also quickens the process of blood regeneration.—J. D. Comrie, Prescriber, Feb., 1935, xxix, 41.

Biliary Disease.—It is generally agreed that bile salts and their derivatives are the most effective stimulants of bile flow, and complimental or substitutional bile salt therapy in biliary disease is becoming a common clinical practice. . . . The conjugated bile acid preparations . . . proved superior as stimulants to the flow of bile containing increased amounts of biliary constituents.—C. R. Schmidt et al., Am. Jour. Digest. Dis., Nov., 1938, v, 613.

Hypertension.—It would therefore appear that these extracts [liver] possess some specific quality which exerts a definite depressor effect upon normal blood pressure in animals and marked hypertension in man.—W. J. Macdonald, Can. Med. Assn. Jour., July, 1925, xv, 697.

Hypertension.—The treatment of hypertension with liver extract brings about a considerable lowering of the blood-pressure and affords complete or marked symptomatic relief in a majority of cases.—T. L. Althausen et al., Am. Jour. Med. Sc., March, 1929, clxxvii, 398.

Hypertension.—Evidences that liver extract is of benefit for reduction of high blood-pressure and to stimulate hepatic detoxication in certain groups of cases associated with toxemia, especially the toxemias of pregnancy, is highly suggestive.—J. F. Halls Dally, Am. Med., June, 1929, xxxv, 353.

Hypertension.—Theoretically, the group of patients who should respond best are those whose hypertension is of brief duration and in whom anatomic alterations have not yet taken place. We have seen many striking and relatively lasting falls of blood pressure in these patients. Such evidence is, however, not convincing. . . . In many patients treated with liver extract, an improvement in symptoms has been the most striking feature noted. In some instances, the improvement in symptoms has been associated with a fall in blood pressure; in other patients, no such fall in pressure has been noted.—R. H. Major, J.A.M.A., July 31, 1926, lxxxvii, 311.

Hypertension.—Liver extract reduces the blood-pressure in cases with kidney diseases, but its effect is not permanent except in rare instances. The general well-being of the patient is usually improved by the continuous administration of liver extract. Liver extract is an adjunct in the treatment of hypertension and of special value where the pressure is at dangerous levels. Liver extract is effective in many cases where nitrites and related vasodilators fail to reduce the blood-pressure.—M. J. Flipse, Jour. Florida Med. Assn., Oct., 1927, xiv, 185.

Hypertension.—The value of liver-extract therapy in hypertension at present is two-fold. From the patient's point of view, it is justified in favorable cases on account of symptomatic relief, which in such cases is unequalled by any therapeutic procedure known heretofore. In cases which respond by lowering of blood pressure, it also serves to take off, or at least to diminish, the extra load imposed on the heart by hypertension. In this way, secondary cardiovascular renal degenerative changes probably can be prevented or their progress slowed down.—T. L. Althausen et al., Am. Jour. Med. Sc., March, 1929, clxxvii, 398.

Hypertension.—During the past three and one-half years I have used Anabolin therapy in a series of 150 cases and have been able, almost without exception, to bring about reasonable symptomatic relief and in a vast majority a very marked reduction in the state of hypertension.—J. D. Willis, Virginia Med. Month., Sept., 1930, lvii, 361.

Pneumonia.—Thirty cases of pneumonia treated with parenteral liver resulted in recovery in 83 per cent. The use of parenteral liver extract was accompanied by a significant rise in the white blood count in all but 2 cases and clinical improvement occurred simultaneously. . . . The treatment is safe, economical, and free from serum sickness. It causes moderate pain at the site of injection.—J. A. Wilson et al., Am. Jour. Med. Sc., June, 1937, cxciii, 752.

Sprue.—The results of treatment, by liver extract, of 2 cases of sprue are reported. . . . Responses similar to those usually obtained in pernicious anemia resulted, with rise in reticulocytes, increase in blood count and improvement of gastrointestinal symptoms with gain in weight and general well-being. Incidentally, it has been pointed out that the typical response may be obtained after a single large dose of liver extract as well as after daily smaller doses.—A. L. Bloomfield et al., Am. Jour. Med. Sc., Feb., 1929, clxxvii, 209.

HARROWER LIVER PRODUCTS

Liver Active Principles

ANABOLIN
Hepatic Detoxicating (Depressor) Principle

Indications: Functional Hypertension; Hepatic Anabolic Insufficiency.

Forms Available: (List Nos. 117A, 117 S) **Sol. Anabolin**—each cc. contains 12 hypotensive units. (Packages of five 1-cc. amp.; also vials of 10 cc.)

(Nos. 118A, 118 S) **Sol. Anabolin Fortior**—each cc. contains 24 hypotensive units. (Packages of five 1-cc. amp.; also vials of 10 cc.)

(No. 117) **Anabolin Tablets**—each contains 1 gr. Detoxicating Hepatic Extract with inert excipient. (Vials of 15; bottles of 50.)

Standardization: Sol. Anabolin is standardized by its influence upon the arterial tension of 10-kg. dogs. Each hypotensive unit is defined as the amount of Anabolin that will give a blood-pressure lowering, as indicated by a kymographic tracing, equal to that caused by 0.083 cc. of a standard depressor solution when compared at that time. By chemical tests, Anabolin is both protein- and histamine-free.

Dose and Administration: In the morning, after taking the blood-pressure, inject 1 cc. intramuscularly. Take the blood-pressure again in the late afternoon, and, depending upon developments, inject 1 cc. or more each day or as advisable. Give 1 tab. q.i.d. with the injections, continuing oral therapy thereafter as indicated. (See also **Isocrine**, page 60.)

HEPARHEMIN (Parenteral)
The Pernicious Anemia Fraction from Liver

Indications: Pernicious Anemia and its complications.

Form Available: (List No. 86A) **Sol. Heparhemin**—each cc. contains the antianemic substance from 100 Gm. fresh liver. (Packages of three 1-cc. amp.)

Dose and Administration: Parenteral only: 1 cc. daily is usually sufficient for maximum reticulocyte response. As maintenance dosage varies greatly, optimum rather than minimum doses are desirable. The maintenance dosage should be regulated by periodic blood studies, although the average requirement is 1 cc. weekly.

LIVER EXTRACT (Harrower)
Parenteral Liver Therapy in Anemia

Indications: Pernicious Anemia, and as part of the treatment of Secondary Anemia; Sprue; Tape-Worm Infestation; X-ray Sickness; etc.

Form Available: (List No. 87 S) **Sol. Liver Extract**—each 10-cc. vial contains 10 U.S.P. injectable liver units. (Vials of 10 cc.)

Standardization: Each cc. represents 1 U.S.P. injectable unit or that amount of material which, when given daily to patients with pernicious anemia, has produced a satisfactory hematopoietic response.

Dose and Administration: Parenteral only (**not** intravenous): From 1 to 5 cc. injected daily or p.r.n.

BILISALIN (Bile Salts)
Highly Purified Conjugated Bile Acid Preparation

Indications: Biliary Stasis; Functional Hepatic Insufficiency; Chronic Constipation with Intestinal Putrefaction; Gall-Bladder Disorders, particularly with evidences of cholesterol stone formation.

Form Available: (List No. 22) **Bilisalin Tablets,** coated—each contains purified Bile Salts gr. 3½; Hepatic Substance q.s. as an excipient. Bilisalin contains no added cathartics. (Bottles of 100.)

Dose and Administration: Oral only: 1 tab. q.i.d. between meals for three days; double dose for three days; treble dose for three days; continue until free bile appears with stool; then omit for three or more days. Repeat this routine several times, lengthening the interval between courses as may be desirable. In cholelithiasis and slow emptying of the gall-bladder: From 2 to 4 tab. t.i.d. for three months or longer.

Contraindications: Obstruction of the hepatic or common ducts.

Compound Liver Formulas

HEMATOCRIN
An Oral Hematinic Formula

Indications: Anemia—hypochromic, nutritional, iron deficiency, hemorrhagic types; Malnutrition; Pregnancy.

Form Available: (List No. 88) **Hematocrin Capsules**—each 7½ gr. contains Heparnucleate (secondary anemia liver fraction with sodium nucleinate) gr. 1½ (representing 45 gr. fresh liver); Exsiccated Ferrous Sulfate gr. 5; Vitamin B Concentrate gr. 1. (Bottles of 100.)

Dose and Administration: Oral only: From 2 to 4 cap. from two to four times a day, preferably with food.

Contraindications: Pernicious Anemia, in which case use **Heparhemin.** (See page 59.)

ISOCRINE (Hepato-Splenic Co.)
A Formula for Use in Chronic Functional Hepatic Defects

Indications: Chronic Hepatic Toxemias; Chronic Diseases with Toxemia; to supplement more direct hepatic-stimulating measures such as Anabolin, Bilisalin, etc.

Form Available: (List No. 5) **Isocrine Tablets**—each 5½ gr. contains Hepatic Substance (1.6) gr. 2½; Anabolin gr. ¼; Spleen Substance (1:4½) gr. 2½; Boldine Hydrochloride gr. 1/60. (Bottles of 100.)

Dose and Administration: Oral only: 1 tab. after each meal and at bedtime. Occasionally this dose may be doubled for seven to ten days. Continue for several months. Use as follow-up treatment after Anabolin in functional hypertension and chronic hepatobiliary insufficiency.

VI.—OVARIAN (ACTIVATING) THERAPY

FOLLOWING the arresting attainments with thyroid feeding, many workers began to use extracts of other glands. In the late 1890's Brown-Sequard published his report regarding testicular organotherapy. About this time Emile Sergent initiated his work with adrenal feeding, while Jayle of Paris (1896) began to use total ovarian extracts.

Ovarian Substance

AT first ovarian feeding was considered as a means of lessening the severity of the common physiologic repercussions of menopausal endocrine realignment, but later it was extended to a much larger list of disturbances based on presumed ovarian irregularities. As always there has been uncritical enthusiasm and unbridled nihilism, and somewhere between these extremes lies the truth. At present ovarian therapy is being somewhat overshadowed by the brilliant achievements of some of its own offspring, such as the progestational hormone and the estrogenic product from pregnancy urine. It is well to remember that, after a cycle of disesteem, crude thyroid is still used rather than thyroxin (Chapter III); also that, although insulin is an indispensable pancreas derivative, it cannot take the place of certain other pancreatic extracts (Chapter IV). We may yet find that ovarian residue has some broader values not fully duplicated in the pregnancy urine, placental, or serum fractions. In a recently published review of endocrinology, Pouchet [1] of Paris says:

"In many cases, observations have shown that total opotherapeutic preparations contain definitely the entirety of the hormones, together with the accessory principles that accompany them in the organ, the role of which is not always negligible, promoting the therapeutic effects that it is desired to produce."

Many conservative and critical clinicians have attested the value of ovarian substance. One of the foremost gynecologists of his day, W. P. Graves,[2] wrote:

"If ovarian substance is proved to be of marked value only in the single instance of treating menopausal symptoms—and in my experience it acts in this respect almost as a specific—ovarian organotherapy hardly deserves the ridicule that has been heaped upon it."

Recalling the reports of Schweitzer and Bainbridge, Cutler [3] gave tablets of ovarian residue by mouth to fifteen patients suffering from painful breasts. Just as Graves regarded ovarian substance as "almost a specific" in menopausal syndromes, so Cutler uses the word "specific" for the effect of ovarian residue in painful breasts. He concludes:

"The administration of ovarian residue apparently tends to cause a cessation of abnormal epithelial and connective tissue hyperplasia by counteracting the excessive corpus luteum secretion, thereby diminishing or removing its overstimulating influence on the breast elements. The administration of ovarian residue by mouth has resulted in relief of pain and tenderness in a number of patients suffering from this condition. A definite softening of the

breasts and actual disappearance of painful nodules have been observed in some cases. The menstrual periods in many are restored to a more normal state and the general state of the patients is improved. The effect of ovarian residue on epithelial and connective tissue changes of the breasts is apparently specific."

Again, Elson [4] describes his results in pruritus vulvae and pruritus senilis following the oral administration of ovarian extract. He believes it to be a specific in these conditions as well as in certain forms of arthritis and neuritis in the aged. It is possible, of course, that keen observers such as these and a large number of other workers have been deceived in the effects that they have ascribed to the oral administration of ovarian residue, but it does not seem likely.

Endovarin is the name given to the Harrower ovarian product, which is freed as far as possible from corpora lutea and prepared for both oral and parenteral use. (See page 72.)

"The Ovarian Trinity"

NOT long after the first therapeutic trials of ovarian feeding, some perceptive clinicians began to recognize the pluriglandular aspects of ovarian dysfunction. By 1913 Dalche, in his clinic at the Hotel Dieu, Paris, was routinely ordering the addition of a moderate dose of thyroid extract to prescriptions for ovarian powder "except in the presence of frank hyperthyroidism." The importance of the thyroid-ovarian cooperation was further corroborated by the findings of Leopold-Levi, and it was from him that the writer received his greatest stimulus to study the value of combined thyroid-ovarian therapy. Even in those early days clinical observation pointed out the relationship of the thyroid to the sex mechanism. That it was particularly important in women was suggested by the facts that goiter is five times more frequent in girls than in boys, that this disorder is comparatively far more common at puberty and at the menopause, and that early hypothyroidism is related to amenorrhea and sterility.

About this time it was shown that the corpus luteum and the ovarian stroma are essentially different organs, especially the corpus luteum of pregnancy. The progestational hormone was not recognized until later. In view of the fact that luteal products are used chiefly for their antiovarian effects, luteal organotherapy is given a chapter by itself (Chapter VII).

The anterior lobe of the pituitary, now sometimes called "the master gland" or "the motor of the ovaries," was not suspected of having any connection with the sex mechanism until Frohlich (1901) observed that obesity and sexual infantilism accompanied pituitary tumor. Other workers noted that severe pressure headaches were often associated with menstrual irregularities, and this was believed to be due to compensatory enlargement of the pituitary gland. (See page 83.) In 1915 the writer suggested the addition of antepituitary extract to the thyroid-ovarian combination recommended by Dalche because it was obvious that the pituitary was involved in most conditions affecting

the thyroid and the ovary. The phrase, "ovarian trinity," came into use at this time, and we began to recognize that this trinity—ovary, thyroid, and pituitary—regulated the endocrine menstrual control.

The Pluriglandular Idea in Gynecology

AT a meeting of the American Gynecological Society in 1919, Graves [5] reported that

"The stimulating effect of the ovarian residue could sometimes be enhanced by the addition of thyroid and the anterior lobe extracts."

This pluriglandular conception was embodied in the Harrower formula now called Menocrin. (Evidence of the synergistic effect of pituitary and thyroid is considered in Chapter VIII.) The combination acts better than either substance alone, and presumably this is true also of ovarian extract in combination with thyroid and pituitary.

The importance of the pluriglandular idea in the understanding and treatment of many dyscrinisms, particularly menstrual and menopausal syndromes, gradually attained wide recognition. Hirst [6] says:

"We are only at the threshold of the problem of all the glands of internal secretion. I believe that future development will be along the lines of pluriglandular therapy, due to the probable correlation between the pituitary, thyroid, mammary gland, suprarenal, and ovary, rather than in the use of single extracts."

The common involvements of members of the ovarian trinity is referred to by many writers. For instance, Frank [7] remarks:

"The three most striking and frequent syndromes encountered have to do with the pituitary, the thyroid, and the ovaries. . . . In the majority of cases, I repeat, the three glands that I have first enumerated will be the ones primarily requiring investigation."

Another statement is that of Wilson,[8] who says:

"For purposes of expediency it is probably better to consider thyroid activity as emanating from the 'thyroid system' instead of a single gland, because of the well-recognized interplay of the thyroid, the pituitary, and the ovary."

In an editorial in the Journal-Lancet [9] the following comment appeared:

"The endocrine substances, thyroid, ovary, and pituitary, offer the opportunity of supplying directly to the patient the principles necessary to initiate menstruation—the same principles which normally are elaborated by the body itself for this purpose."

Again, in an answer to a query in the Journal of the American Medical Association,[10] this statement is made:

"Most cases of secondary amenorrhea result from an aberration in the function of one or more ductless glands. The glands usually involved are the pituitary, the ovaries, and the thyroid. It is usually difficult to detect the responsible one."

More recently, in his excellent book, Kurzrok [11] states:

"An interrelationship exists between the thyroid gland and the adenohypophysis that is similar to that between the latter gland and the gonads. . . . It has been known clinically that the thyroid gland enlarges during puberty,

menstruation, lactation, and pregnancy. The nature of the interrelationship is still uncertain, but it is more than likely that it is through the mediation of the anterior pituitary gland."

Menocrin

THE original pluriglandular ovarian formula, Thyro-Ovarian Co. (Harrower), now called Menocrin, was offered as a means of regulating the menstrual endocrine control. This formula consists of ovarian residue, antepituitary, and Endothyrin. (See page 30.) Time and experience have proved its value, while the statements quoted, and many others, confirm its rationale.

When Zondek called the antepituitary "the motor of the sex mechanism," he used an apt metaphor. We might carry the figure a bit further and call the thyroid the carburetor and the essential (ovarian) sex cells the fuel. These three endocrines depend closely upon one another. If one fails, they all fail, and the outcome is a disturbed sexual cycle. Therefore, in Hancher and Rogers' [12] words, "The reasons for combining ovarian with thyroid or pituitary feeding are quite obvious."

It is not for a moment suggested that other glands in addition to the pituitary, thyroid, and ovary are never involved in menstrual and menopausal disorders, but experience has demonstrated that a balanced pituitary-thyroid-ovary combination such as Menocrin is sound background therapy in these conditions. It is a rational physiologic method of correcting endocrine disequilibrium in disorders of the female sex cycle.

There are two modifications of this formula that are more suited to the control of certain commonly related syndromes. When hypoadrenia is also present, or in asthenic dysovarism where the menopause or menstrual disorder is accompanied with a predominating fatigue syndrome, the "ovarian trinity" is supplemented with adrenal cortex. This formula is known as Menocrin Fortior. (See page 74.)

In the presence of amenorrhea accompanied with utero-ovarian hypoplasia and perhaps other symptoms of pituitary involvement, the Menocrin formula with the amount of the pituitary ingredient increased six times, as well as the addition of gonadotropic material from the male gonads, makes a broader and more potent agent. This formula is known as Govarin. (See page 74.) Both these formulas are given in much the same way as Menocrin.

The indications for Menocrin include a large number of commonplace menstrual and menopausal disorders that are founded upon the disturbances of the endocrine control of these functions:

Young Girls: Failure or difficulty in establishing the menstrual cycles.

Adult Women: Menstrual irregularities, amenorrhea, dysmenorrhea, frigidity, endocrine sterility, etc.

Middle-Aged Women: Menopausal disorders, and nervous and mental symptoms of this period.

The basic fault may be the same in any of these lesions (disturbances based on organic lesions are excluded here). Carrying Zondek's metaphor

still further we might say that the regulators of the ovarian cycle are "out of gear."

Obesity is often a problem of the menopause. Usually it is a thyro-pituitary condition and, when based upon deranged endocrine correlation, is likely to be responsive to indicated organotherapy. The subject is given further consideration in Chapter VIII.

There are also a number of seemingly unrelated conditions, such as asthma, arthritis, allergic syndromes, dermatoses, gastric upsets, epilepsy, migraine, etc., which may show a tendency to occur at or near the menses and at the onset of the menopause. When conditions of this kind exhibit a menstrual periodicity or seem to be exacerbated during menstruation, pluriglandular therapy, as with Menocrin or one of its modifications, should be considered.

This is in no sense to discount the importance of the more highly purified active principles, such as estrogenic substance (Plestrin), the progestational hormone (Endoluteum in Oil), and the anterior pituitary-like gonadotropic hormone (APestrin). Indeed, one or more of these products are frequently indicated to supplement Menocrin. It must be remembered, however, that they have a purely substitutive effect, and also that the protracted administration of highly concentrated estrins is not unattended with hazards. Many experienced clinicians have found Menocrin adequate for the average case. For advanced cases in which rapid results are required, they use Menocrin or one of its modifications orally as "background therapy" directed at the basic pluriglandular disequilibrium, and supplement this with injections of Plestrin, Endoluteum, or APestrin according to indications. From long clinical observation it appears that, with suitable Menocrin therapy, considerably less of these products is required. A cyclic method of dosage has been found advantageous. (See page 73.)

The Estrogenic Hormones

THE first product of this type, and we believe it was the first available to the medical profession in this country, was offered by Harrower in 1926 under the name Folliculin. It was made from the liquor folliculi of bovine ovaries. Less than a year later, following the early work of Dodds and his associates in England, we began the extraction of this product from placenta. At the same time its name was changed to Plestrin (a contraction of placental estrin). At first this product was an aqueous extract containing 5 rat units per cubic centimeter, which later was increased to 50 rat units. The chemical identification of this hormone and improved methods of extraction enable us now to offer a crystalline hormone (ketohydroxyestrin) which, dissolved in a light oil, is available in concentrations of 2,000, 5,000, and 10,000 I.U. per cubic centimeter. (For information on units of potency, see page 117.)

The most readily demonstrable action of the estrogenic hormone is stimulation of the epithelium of the female generative system, including the mam-

mary glands but excluding the germinal layer of the ovaries. Apparently estrin is necessary for the proper development of the secondary sex characteristics; the menstrual cycle also is partly dependent upon it. Estrin therapy in adequate dosage is of value in preventing and overcoming the atrophic effects of castration on the genital tract and breasts. It also confers symptomatic relief when given for the symptoms of the artificial or natural menopause. Plestrin is indicated in a wide variety of cases, the common etiologic denominator being a lowering of the estrin level of the blood, a factor that can now be estimated with considerable precision.

No definite dosage can be given for this type of therapy, the quantity of estrin being essentially dependent upon the difference between the amount of estrogenic hormone already present (or being produced) and the supply that is necessary for normal health.

The amount of estrin and progesterone required for the production of a complete cycle in a castrate or in primary amenorrhea has been computed by Kaufmann [13] to be 200,000 mouse units of estrin and from 35 to 50 rabbit units of progesterone. This figure is considered low by other investigators,[14] who calculate that for the human a complete replacement therapy would require the subcutaneous administration of 500,000 M.U. (approximately the same number of international units) of estrin. "Background" combined hormone therapy as with Menocrin, the results of which include a greater increase in the ovarian activity, seems to diminish greatly the required dosage of estrin. Moreover, the use of Menocrin in this way seems eminently rational, since, as we have seen, the etiology of these disorders is rarely a pure estrin deficiency. In most cases there is a pituitary-thyroid-ovarian imbalance.

The usual test for the efficacy of estrin therapy, i.e., its effect on the vaginal mucosa (see Appendix, Section 6), cannot be considered an accurate method of estimating the necessary dosage. For instance, Marrian and Parkes [15] state that, while 1 M.U. of estrin produces a cornified vaginal epithelium, 200 M.U. is required to duplicate all the phenomena of the estrous cycle. Therefore, the dosage necessary for adequate effect will be the difference between the quantity of estrin present and the figures cited. In the more serious conditions, such as menopausal syndromes, particularly menopausal arthritis and psychosis, many times this dose may be necessary. When an adequate concentration of estrin has been built up and the symptoms brought under control, it is possible rapidly to reduce the dosage to a maintenance level that will sustain the patient comfortably. Most failures with estrin therapy have been due to inadequate dosage, particularly at the beginning of the treatment. Suggestions regarding the dosage of estrogenic hormones will be found on pages 72 and 73.

The general indications for Plestrin therapy are: menopausal syndromes, hypomenorrhea, oligomenorrhea, amenorrhea, mastopathy, mastodynia, some dermatoses, pruritus, kraurosis, senile vaginitis, migraine, neuralgia, and some cases of retinitis pigmentosa and iridocyclitis.

Oral Estrin Therapy

DESPITE the fact that the estrins are demonstrably less active when given orally than parenterally, these crystalline extractives are nevertheless potent when given by mouth, and many clinical as well as experimental reports confirm this. For example, referring to this therapy, Young [16] states:

"In the typical vasomotor disturbances of the climacteric, four tablets (each 1,000 international units) of oestrone taken daily by mouth should be the initial dosage, increased by one tablet daily after a week's trial until the symptoms are controlled. It is important, from the standpoint both of expense and of convenience, for the practitioner to realize that many menopausal cases respond well to oral administration."

Another interesting report by Bishop [17] is more than a statement of clinical conclusions, for it happens that the author took pains to make careful estimations of the estrin levels in the blood before and after such therapy. He says:

"Administration of oestrin in quite small doses by mouth was effective in controlling symptoms. The level of oestrone threshold bleeding was found to be between 5,000 and 6,000 I.U. by injection and 25,000 and 30,000 I.U. by mouth, suggesting a peroral/intramuscular ratio of 5:1."

The Harrower product for the application of oral estrin therapy is known as Plestrin Oral, and is available in two strengths: 1,000 and 2,000 I.U. per capsule. (See page 72.) It is most commonly used as a supplement to pluriglandular therapy, as with Menocrin, or to parenteral therapy with Plestrin in Oil. A sound method is to commence estrin replacement aggressively by injecting Plestrin (2,000-10,000 I.U. daily), thus promptly raising the estrin level, and then to use Plestrin Oral as maintenance therapy, for oral administration is more suitable for the prolonged treatment usually required. Dosage must be individualized, but from 2,000 to 4,000 I.U. a day has decided value and prolongs the benefits attained by the other means mentioned earlier in this chapter.

Plestrin as a Pharmacodynamic Agent

SEVERAL of the uses of Plestrin are considerably beyond the regulation of dysovarism and its long list of dependent symptoms. Since estrin therapy artificially raises the serum-estrin content, it may be used in several conditions in which a high estrin level is advantageous. For example, Ramos and Colombo [18] found that the final changes in the breasts leading to lactation are inhibited by estrin. These authors reported fifty cases successfully treated with estrogenic hormone (injections of 10,000 I.U. daily for three or four days). If the injections are begun immediately after delivery, no other treatment is necessary. A warning is given that estrin should never be used before labor as it may interfere with the initiation of lactation.

Foss and Phillips [19] believe that estrin exerts a specific effect on the mammae, for they found that lactation can be suppressed satisfactorily by the oral administration of a total of from 20,000 to 30,000 I.U. given in divided doses over a period of from two to six days.

Another application of this virtual pharmacodynamic effect was suggested by Engelhart,[20] who reports success from the daily administration of 10,000 I.U. of estrin in puerperal sepsis. In severe cases with rigor and chill, 50,000 I.U. was given. Engelhart treated a number of cases with outstanding benefit and suggests that this effect probably was based upon the influence of such therapy on uterine hyperemia, which creates a more favorable antibacterial defense because of the increased amount of blood brought to the tissues involved. Presumably this treatment would also interfere with lactation.

Perhaps a similar action assists the epithelium-maturing effect of estrins in the treatment of vaginitis in children as well as in the aged. There are many astonishing reports of this remarkable development in genitourinary practice, but it must suffice here to give only one excerpt. Sir Frederick Menzies,[21] in an official report from the London Medical Officer of Health has this to say:

"Many observers have reported favourably on the use of oestrin. Oestrin can be given by mouth, by injection, or in the form of suppositories, the dosage being approximately five times as great by mouth as by injection. The oral method is probably to be preferred as children do not object to it, and the daily insertion of a vaginal suppository is considered undesirable. The daily dose is 3,000 to 6,000 units, according to the size of the child, and it may be given at one time, say every morning."

Still another aspect of this phase of estrin therapy has been developed recently. Blaisdell [22] reports benefit in ozena from the local application of estrin in oil. His procedure was simple: Once a week 1 cc. of the oily solution (containing 10,000 I.U. per cc.) was dropped into the nares and held in contact with the affected mucous membrane. After six or eight such applications, treatment was continued at two-, four-, or six-week intervals. Additional high unitage solution may be sprayed into the nose t.i.d. It is claimed that this controls the condition better than any other treatment used. Indeed, Collip and coworkers [23] conclude that

"In estrogenic hormone insufflation there is to be found a therapy for ozaena and atrophic rhinitis considerably more effective than any other till now available."

The Anterior Pituitary-Like Hormone

THE first source of gonadotropic hormone was the anterior lobe of the pituitary. This proved an unsatisfactory source for several reasons—notably the small amount that could be obtained, its extreme expense, and also the marked thermolability of the product. Later it was found that pregnancy urine was a good source, and still later the placenta was found to be a rich storehouse of gonadotropic substance. The action of these extracts resembles that of the anterior pituitary gonadotropic hormone so closely that they are generally designated as "anterior pituitary-like" gonadotropic hormones.

The Harrower Laboratory offers APestrin, an active, highly purified, chorionic gonadotropic principle, containing both luteinizing and follicle-stimulating hormones. It is physiologically standardized. (See Appendix, Section 6.)

It must be remembered that products of this type are effective only in those patients whose gonads are intact and capable of responding. This is not the case, however, with Plestrin which, as has been emphasized, is purely substitutive therapy. APestrin stimulates follicle ripening (it is advantageous to add equal amounts of Sol. Pituitary Co.—Harrower for this purpose), liberation of estrin, ovulation, and luteinization with associated effects upon the secondary sex characteristics.

The general indications for the use of APestrin are: functional uterine bleeding, premature menopause, secondary amenorrhea, dysmenorrhea, delayed puberty, infantilism, cryptorchidism, and the adiposogenital dystrophy. Reports from the literature indicate that this type of product has been used with success also in habitual and threatened abortion, certain types of sterility (apparently due to ovarian or testicular dysfunction), acne vulgaris, and the lesser forms of pituitary cachexia. The dosage cannot be stated arbitrarily; generally from 100 to 500 rat units is injected daily or every other day. In some conditions a cyclic method of dosage is advisable. APestrin is contraindicated in uterine bleeding caused by pelvic inflammatory disease. The possibility of infection, neoplasm, or other pathologic lesions should be excluded carefully before beginning treatment with products of this type.

[Note: Since corpus luteum and progesterone are definitely antiovarian in effect, they are discussed in the next chapter on Luteal (Antiovarian) Therapy.]

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OVARIAN—CLINICAL EXCERPTS

Amenorrhea.—To pass to another type of ovarian dysfunction, amenorrhea furnishes a good illustration of the multiplicity of factors which may operate to bring about the same clinical symptom, emphasizing the absurdity of the old rule-of-thumb plans of treating menstrual disorders. The three endocrine glands most frequently concerned are the ovary, the pituitary, and the thyroid, but it is not easy always to localize the primary cause, or to tell why it should occur.—Emil Novak, Am. Jour. Obst. and Gynec., Aug., 1937, xxxiv, 237.

Amenorrhea.—Most cases of secondary amenorrhea result from an aberration in the function of one or more ductless glands. The glands usually involved are the pituitary, the ovaries, and the thyroid. It is usually difficult to detect the responsible one.—Queries, J.A.M.A., June 9, 1934, cii, 1963.

Amenorrhea.—In general, it may be said that histories of primary amenorrhea, amenorrhea following after a few months or years of reasonably regular cyclic flowing, scanty menstruation, irregular menstruation and menorrhagia are all to be considered as evidences of subnormal intensity of pituitary stimulation of the ovaries.—E. L. Sevringhaus (Book, see Appendix) page 149.

Amenorrhea.—The dosage of estrogen in amenorrhea should be that amount which will raise and maintain the quantity of circulating estrogen to the normal premenstrual level. When administered for this purpose, estrogen is best given orally in doses of from 1000 to 2000 I.U. daily for 8 to 12 weeks. Ample data have accumulated proving the effectiveness of orally administered estrogens. The chief advantage of the oral route, aside from the economic factor, is that it more closely imitates nature by supplying small quantities of the hormone continuously.—S. Leon Israel, Endocrinology, Feb., 1938, xxii, 253.

Menopause.—Cessation of ovarian function (hypofunction) is the primary causative factor. The withdrawal of the ovarian hormone simply initiates the endocrine disturbance and the symptoms accompanying it are probably due to hyper- or hypofunction of other endocrine organs (thyroid, adrenal and pituitary) with hyperfunction of the pituitary as probably the most noticeable change.—H. Swanberg, Illinois Med. Jour., Nov., 1937, lxxii, 441.

Menopausal Syndromes.—When symptoms are mild the beneficial effect of even small doses of oestrin (3,000 international units, or 0.3 mg., of oestrone by mouth each day) is often immediately apparent. Such patients not only profess to feel more composed and "consolidated," but not infrequently discontinue spontaneously a long-standing barbiturate habit. In all cases the dose of the latter which is necessary for sleep may be progressively reduced.—H. R. Donald, Brit. Med. Jour., Nov. 6, 1937, 899.

Menopause, Surgical.—Thus it would appear that relatively small doses of oestrin by mouth are effective in controlling the symptoms of acute ovarian deficiency in a castrate.—P. M. F. Bishop, Brit. Med. Jour., April 30, 1938, 939.

Menopause.—The tradition that they [distressing symptoms during menopause] must be borne is unsound, for the administration of estrogenic preparations is rational and relieves the symptoms in a great majority of cases. Involution melancholia, pruritus vulvae, senile vaginitis and menopausal hypertension are also frequently relieved by estrogens. . . . Treatment should be instituted as soon as symptoms appear. Dosage must be adequate and treatment should be continued until the patient remains free from symptoms without therapy. Higher doses are usually required in patients with artificial menopause.—L. F. Hawkinson, J.A.M.A., July 30, 1938, cxi, 390.

Menopausal Rheumatism.—The menopause is a very frequent cause of rheumatism. Its forms are manifold and sometimes really serious. Nothing can show the relationship between rheumatism and ovarian dysfunction more clearly than the occurrence of rheumatism after surgical or radio-therapeutic suppression of ovarian activity, facts which cannot be disputed. . . . In all types of rheumatism of the menopause, organic preparations are of value, both ovarian and pluriglandular.—Editorial, Bruxelles-med., Oct. 14, 1928, viii, 1629.

Menorrhagia.—Whatever the degree of ovarian failure, a careful examination of the patient will usually reveal evidence of some endocrine disturbance. The most common offenders are the pituitary, the thyroid, and the ovary. . . . Functional menorrhagia and metrorrhagia, therefore, are symptoms of an ovarian disturbance, either primary or secondary to diseases of the pituitary or thyroid, or secondary to some constitutional disease affecting one or more components of the endocrine system.—J. C. Burch et al., J.A.M.A., Dec. 4, 1937, cix, 1869.

Ovarian Epilepsy.—Two cases of severe epilepsy were striking for they reacted promptly to ovarian hormone therapy and the epileptic attacks ceased. In both cases there was an inevitable association with menstruation, that is dysmenorrhea and oligomenorrhea. The therapy instituted in both these instances had very satisfactory effects.—G. Kausch, Munchen. med. Wchnschr., June, 1934, lxxxi, 977.

Sterility.—These relationships which the various incretions bear to the sex function offer a basis for treatment of quite a large group of women suffering from sterility. Ovarian extracts should be employed in these cases of diminished sex function, but alone will rarely produce satisfactory results. If the relationship of the thyroid and the pituitary to the condition under observation is carefully diagnosed and the indicated incretion added, then success will very often follow the treatment.—F. M. Pottenger, Calif. State Jour. Med., Nov., 1923, xxi, 465.

Sterility.—. . . the thyroid, which is a very definite factor in the physiology of reproduction. Therefore, in the diagnosis of the causes of infertility, sterility, and abortion, one must investigate the three glands most frequently involved—the pituitary, the ovaries, and the thyroid.—J. C. Litzenberg, J.A.M.A., Dec. 4, 1937, cix, 1871.

Vaginitis in Children.—From the results obtained it is believed that theelin, or a similar estrogenic substance, is the treatment of choice in gonococcal vaginitis in children. It is apparently safe and effective in both acute and chronic cases. For reasons not clear the chronic cases respond more promptly to treatment than do the acute infections.—B. Reading, South. Med. Jour., May, 1935, xxviii, 464.

Vaginitis, Senile.—From the results of treatment of senile vaginitis with these substances [estrogenic], it is evident that the shedding and re-formation of the mucosa eliminate the underlying pathology present in vaginitis. The normal mucosa thus produced is better able to resist those factors, whether of infectious or atrophic character, which cause the vaginitis. In this way a cure is brought about. Even when a cure is not complete, the relief of symptoms justifies the use of estrogenic substances in the treatment of senile vaginitis.—A. Jacoby et al., Am. Jour. Obst. and Gynec., April, 1936, xxxi, 654.

Vomiting of Pregnancy.—Nearly 100 additional cases [hyperemesis gravidarum] have been treated [with estrogen] in the last two and one-half years and the results continue to be excellent. In severe cases daily injections of 10,000 international units of estrogen in oil are given.—Queries and Minor Notes, L. F. Hawkinson, J.A.M.A., Sept. 24, 1938, cxi, 1235.

HARROWER OVARIAN (ACTIVATING) PRODUCTS

APESTRIN

Chorionic Gonadotropic (A.P.L.) Hormone

Indications: Hypogenitalism; Infantilism; Hypovarism; Amenorrhea; Functional Uterine Bleeding; Sterility in both sexes; Cryptorchidism.

Form Available: (List No. 160 S) **Sol. APestrin**—each cc. contains not less than 500 rat units of the chorionic gonadotropic hormone. (Vials of 10 cc.)

Standardization: One rat unit is defined as the smallest amount of solution that, given in six equal subcutaneous doses for a period of three days (two injections daily), will mature immature female white rats thirty days old.

Dose and Administration: Parenteral only: From 100 to 500 rat units daily for seven to ten days, then every second or third day for some weeks. May be supplemented with **Pediacrin** (see page 96) in developmental defects in children; or with **Govarin** (see page 74) in sterility and utero-ovarian hypoplasia, etc.

ENDOVARIN

Bovine Ovarian Extract

Indications: Ovarian Insufficiency; Menopause; etc.

Forms Available: (List No. 121) **Endovarin Tablets**—each 5 gr. contains Ovarian Residue (N.F. VI) gr. 2, equivalent to 12 gr. of fresh bovine ovarian tissue freed as far as possible from corpus luteum. (Bottles of 50.)

(No. 121A, 121 S) **Sol. Endovarin**—each cc. contains the water-soluble active material from 40 gr. fresh ovaries, freed as far as possible from corpus luteum. (Packages of five 1-cc. amp.; also vials of 10 cc.)

Dose and Administration: Oral: From 1 to 3 tab. t.i.d.; double dosage occasionally. (Cyclic dosage is preferable—see under **Menocrin**, page 73.) Parenteral: 1 cc. daily or every other day.

PLESTRIN in OIL (Folliculin; Placental Estrin)

Estrogenic Hormone

Indications: Hypoestrinemia; Functional Amenorrhea and Dysmenorrhea; Vasomotor Symptoms of Natural or Surgical Menopause; Functional Hypogonadism with Asexualism, Frigidity, and Endocrine Sterility; Vaginitis in Children and Aged; Certain Mental and Nervous Disorders of Ovarian Origin; etc.

Forms Available: An oily solution standardized in International Units:

(List No. 145A) **Plestrin in Oil**—2,000 I.U. per cc. (Boxes of 5 and 100 1-cc. amp.)

(No. 146A) **Plestrin in Oil**—5,000 I.U. per cc. (Boxes of 5 and 100 1-cc. amp.)

(No. 146S) **Plestrin in Oil**—5,000 I.U. per cc. (Vials of 10 cc.)

(No. 147A) **Plestrin in Oil**—10,000 I.U. per cc. (Boxes of 5 and 100 1-cc. amp.)

(No. 147S) **Plestrin in Oil**—10,000 I.U. per cc. (Vials of 10 cc.)

(Nos. 150, 151) **Plestrin Oral**—each capsule contains 1,000 I.U. (No. 150) or 2,000 I.U. (No. 151). (Bottles of 40 and 100 of both strengths.)

Standardization: Standardized in International Units. One I.U. is defined by the League of Nations Health Organization as the specific estrus-producing activity contained in 0.1 gamma (0.0001 mg.) of the standard crystalline ketohydroxyestrin. The capsules contain a concentrate of the naturally occurring estrogenic substances, biologically assayed by the vaginal smear method. (See page 117.)

Dose and Administration: Parenteral: **Plestrin in Oil**—Dosage is best guided by periodic determination of estrin level in the blood. In practice, dosage is usually determined by clinical response. Average dosage for various disorders is as follows:

Menopausal Syndrome (Natural or Surgical)—25,000 to 50,000 I.U. weekly in acute cases until symptomatic relief is obtained; decrease gradually to maintenance dose. Usual maintenance dose is 2,000 I.U. two or three times weekly.
Hypomenorrhea, Oligomenorrhea—10,000 to 25,000 I.U. weekly during first half of menstrual cycle.
Amenorrhea (Primary)—25,000 to 50,000 I.U. weekly.
Amenorrhea (Secondary)—10,000 I.U. at four-day intervals for six injections. Omit for ten days; repeat for several months if necessary.
Mastopathy (Chronic Mastitis, Mastodynia, Mazoplasia, etc.)—2,000 to 5,000 I.U. for several injections previous to and during period of symptoms.
Inhibiting Lactation—20,000 to 40,000 I.U. during first three days postpartum.
Dermatoses (Acne, Eczema, etc.)—1,000 I.U. daily or 2,000 I.U. every other day.
Menopausal Arthritis—10,000 to 25,000 I.U. two or three times weekly.
Vulvovaginitis (Specific or Non-Specific, Children)—1,000 to 2,000 I.U. daily until four negative weekly smears are obtained.
Senile Vaginitis, Pruritus, Kraurosis—5,000 to 10,000 I.U. three times weekly.

Oral: **Plestrin Oral**—From 1,000 to 3,000 I.U. t.i.d. May be desirable to continue therapy after initial course of injections, or to supplement oral therapy with pluriglandular formulas such as **Menocrin** or **Govarin** (see below).

Pluriglandular Ovarian Formulas

MENOCRIN (Thyro-Ovarian Co.)

A Balanced Combination of Ovary, Thyroid, and Antepituitary

Indications: Menstrual Disorders; Amenorrhea; Dysmenorrhea; Mastodynia; Menopausal Syndromes; Sexual Neuroses.

Forms Available: (List No. 4) **Menocrin Tablets** (or Capsules)—each 5 gr. contains Ovarian Residue (N.F. VI) gr. 3; Anterior Pituitary (N.F. VI) gr. ¼; Endothyrin gr. 1/12; Calcisalin (excipient) q.s. (Bottles of 100.)

(Nos. 4A, 4S) **Sol. Menocrin**—each cc. contains the water-soluble active material from 20 gr. fresh glands in the proportions: Ovary 36, Antepituitary 3, Thyroid 3. (Packages of 5 and 100 1-cc. amp.; also vials of 10 cc.)

(No. 4D) **Menocrin Drops** (Glycerite)—each cc. contains the glycerin-soluble ingredients from 72 gr. fresh glands in the proportions: Ovary 62, Thyroid 5, Antepituitary 5. For dosage purposes 1 cc. (16 min.) equals two 5-gr. tablets. (Dropper bottles of 25 cc.)

Dose and Administration: Oral: 2 tab. (or cap.) q.i.d. for ten days before menses (or molimen); omit for ten days at onset; 1 q.i.d. until ten days before next menses; repeat for several periods. Drops: From 10 to 15 min. in cyclic dosage suggested above, as a variant in place of tablets where treatment must be given for months, e.g., during the menopause. Parenteral: 1 cc. daily or every other day, preferably grouped in series given during heavier oral dosage. In menstrual and menopausal syndromes with definite lowering of estrogenic hormone level, supplement with **Plestrin in Oil.**

Contraindications: Pregnancy; Hyperovarism; Hyperthyroidism.

MENOCRIN FORTIOR (Adreno-Ovarian Co.)
Menocrin plus Adrenal Cortex

Indications: Ovarian Dysfunction; Menstrual and Menopausal Disorders associated with Asthenia, Hypotension, and Depletion.

Form Available: (List No. 79) **Menocrin Fortior Tablets** (or Capsules)—each 5 gr. contains the Menocrin formula (page 73) gr. 4; Adrenal Cortex Substance gr. 1. (Bottles of 100.)

Dose and Administration: Oral: 2 tab. (or cap.) q.i.d. for ten days before menses (or molimen); omit for ten days at onset; 1 q.i.d. until ten days before next menses; repeat for several periods. Parenteral: When injections are desirable give **Plestrin,** from 2,000 to 10,000 I.U. daily (see page 72) to raise the estrin level and/or **Sol. Adreno-Cortin,** from 1 to 3 cc. daily, for its supportive effect. (See page 22.)

Contraindications: Pregnancy; Hyperthyroidism; Hypertension.

GOVARIN (Gonad-Ovarian Co.)
Menocrin with added Antepituitary and Gonad Extracts

Indications: Hypovarism; Amenorrhea; Infantilism; Utero-Ovarian Hypoplasia; Hypopituitarism.

Form Available: (List No. 73) **Govarin Tablets**—each 6 gr. contains the Menocrin formula (page 73) gr. 3; Anterior Pituitary (N.F. VI) gr. 1½; Orchic Substance (1:9) gr. 1½. (Bottles of 100.)

Dose and Administration: Oral: Since menstruation is often absent in these cases, divide the month into three equal parts, giving 2 tab. q.i.d. for ten days; 1 q.i.d. for ten days; omit for rest of month; repeat for many months. When there is a molimen or trace of menstrual flow, rearrange dosage schedule so that heavy dose is given during the ten days before expected catamenia. Parenteral: Supplementary injections are desirable in advanced lesions of this kind. Alternate between courses of **APestrin,** from 100 to 500 rat units daily or every other day (see page 72), and **Sol. Pituitary Co.,** 1 or 2 cc. daily or every other day. (See page 95.) These gonadotropic solutions may be given together, and it is best to omit the injections during the suggested periods of reduced oral dosage.

MATHOCRIN (Mamma-Ovary Co.)
Ovarian Regulation in Early Menorrhagias

Indications: Dysovarism with Menorrhagia; Mastodynia; Prolonged Menses in Girls.

Form Available: (List No. 38) **Mathocrin Tablets**—each 5 gr. contains Mammary Substance gr. 2½; Ovarian Residue (N.F. VI) gr. 1; Endothyrin gr. 1/12; Calcisalin (excipient) q.s. (Bottles of 100.)

Dose and Administration: Oral only: 1 tab. q.i.d.; double dose three days before and during menses; omit for one week; repeat for at least three periods. In severe cases, may be supplemented with injections of **APestrin,** from ½ to 1 cc. daily or every other day during heavier oral dosage.

THYRO-PANCREAS CO. w. OVARY
Ovary, Pancreas, Thyroid

Indications: Hypertension with Hypothyroidism, especially at the Menopause. (See Chapter III.)

SYDOCRIN (Pancreas Co.)
Ovary, Pancreas, Adrenal, Pituitary

Indications: Hyperthyroidism; Sympathetic Irritability; Dysovarism with Thyroid Sensitiveness. (See page 47.)

VII—LUTEAL (ANTIOVARIAN) THERAPY

ANTIOVARIAN therapy leads at once to a consideration of the chalones, or those opposing endocrine principles whose chief service is to neutralize or balance the stimulating effects of the hormones. As a general rule, what might be called negative or inhibitory organotherapy is not so satisfactory as positive or activating therapy.

There are three glandular spheres of influence that tend to oppose or overrule the ovarian functions: the corpus luteum, the antepituitary, and the mammary glands.

The Corpus Luteum Hormones

FOR a long time corpus luteum was given with the remainder of the ovarian tissue without a proper understanding that the follicular (estrogenic) hormone was not only different from the luteal (luteinizing) hormone, but actually its antagonist. Hisaw and others [1] were among the first to show that the luteal hormone inhibits the estrous cycle, ovulation, and menstruation. After conception, when the much larger and more active corpus luteum of pregnancy comes into existence, this antiovarian effect is so marked that ovulation is stopped and ovarian activity overruled. The luteal hormone is, therefore, a true chalone (endocrine inhibitor) of the follicular hormone and has been proved by Corner [2] to be responsible for the production of progestational proliferation of the endometrium—hence it is called "progestin." Menstruation normally follows the withdrawal of progestin.

The removal of the corpora lutea from experimental animals early in pregnancy results in abortion.[3] This is because one of the functions of the corpus luteum hormone is to assist in maintaining adequate nutrition of the placenta.

Among the early workers with corpus luteum hormone therapy is Fluhmann [4] who, referring to previous clinical trials, said:

". . . recent preliminary studies also point to the successful use of 'luteinizing' extracts in the control of the uterine hemorrhage accompanying hyperplasia of the endometrium."

For years crude corpus luteum preparations, and later active luteal fractions, have been used in the treatment of ovarian overactivity or ovarian irritability. They are of prospective value when the luteal activities are insufficient to overrule the ovarian function. This occurs in certain problems of early pregnancy, particularly the tendency to abortion and attempts at menstruation. Smith and Smith [5] report that

"The luteinizing hormone which stimulates the production of progestin has been administered, with promising results, to nineteen patients whose chief symptom was abnormal flowing."

Progestin is considered by some authorities [6] to be the true corpus luteum hormone. Physiologically, progestin apparently brings about progesta-

tional proliferation of the endometrium, promoting the change from the proliferative to the secretory stage. The corpus luteum hormone also inhibits uterine contractions, an action that can often be used to advantage during late pregnancy.[7]

There are at least two endocrine principles of luteal origin. An aqueous extract of the corpus luteum has been demonstrated by Macht and his coworkers [8, 9] to have definite antiovarian effects, by its ability to prolong the interestrous period in experimental animals. In their first series of experiments, the average duration of the period for guinea-pigs receiving injections of aqueous luteal extract was thirty-seven days—a prolongation of the average time by 187 per cent. In a second series the results were confirmed, with the prolongation of the interestrous period 157 per cent. Macht [9] concludes that

". . . injections of such extracts prolong the interoestrous period, and also shorten the duration of the oestrus when it occurs. This was learned from microscopical examination of vaginal smears and also through anatomical studies. These results seem to be in perfect accord with the original theories of Fraenkel and Loeb who held that one of the functions of the corpus luteum was to inhibit ovulation."

The Harrower product, Endoluteum, may be given to normal female rats with definite prolongation of the interestrous period.

On the other hand, the so-called progestational hormone is lipid in character and, therefore, is available only in an oily solution. The antestrous effect can be obtained from the Harrower aqueous extract, Endoluteum, while the progestational hormone is represented by Endoluteum in Oil. (See page 81.) The differences between these preparations are not precisely known, some workers believing that progestin is partially water-soluble, though clinically they appear to have separate values. The natural and original source of the corpus luteum hormone was the corpora lutea of animals, and the domestic pig is ideal because it ovulates frequently and from many follicles. Endoluteum in Oil is a solution of the natural progestational hormone, standardized to contain ½ international unit per cubic centimeter. The synthetic progestin is made from stigmasterol, a sterol derived from soy-beans. (See Appendix, Section 2.)

Close Interglandular Relationships

PART of the influence of the luteal hormones is upon and through the anterior lobe of the pituitary, which also produces an estrus-inhibiting principle. Whether the corpus luteum stimulates the pituitary and the two related products bring about their effects together, or whether the luteinizing hormone of the pituitary stimulates the corpus luteum is not clearly understood. By administering corpus luteum extracts of cows to mice, Patel [10] was able to inhibit estrus, prevent abortion, and maintain gestation. Of these experiments, he said:

"Kythin [Wiesner and Patel's corpus luteum extract containing a factor responsible for the maintenance of gestation] inhibits oestrus by producing pseudo-pregnancy conditions in the injected mice. The inhibition of oestrin

can be obtained for a long period . . . without causing any permanent injury to the ovaries. . . . It is probable that the kythin also acts on the pituitary, inhibiting the secretion of the oestrogenic substance of the pituitary—a condition similar to that found during pregnancy."

The Antepituitary Luteinizing Hormone

ONE important principle contributed by the anterior lobe of the pituitary stimulates maturation and luteinization of the graafian follicles. This is produced in a cyclic fashion, its output waxing and waning with the ovarian cycle.

An extract in which this active principle is largely separated from the growth and gonadotropic fractions (see Chapter VIII) is used as a means of depressing ovarian follicular function. As a result of the work of Collip[11] it is now possible to obtain a substance with a similar action from the placenta and pregnancy urine.

The antepituitary substance may be used to supplement the antestrous effects of Endoluteum. Like the luteal extract referred to above, it has been found capable of prolonging the interestrous periods of albino rats. This luteinizing fraction is included in a pluriglandular antiovarian formula (Chalomen), each dose-unit containing the equivalent of the amount required to produce luteinization of the ovaries of the mature rabbit.

The Basis for Mammary Therapy

YEARS before the antiovarian products from the corpus luteum and antepituitary were available, it was known from clinical work that the mamme exerts an antiovarian influence and that mammary extracts lessen the menstrual flow, particularly in menorrhagia at the menopause. For example, in his "Principles of Therapeutics," Osborne [12] remarks:

". . . the administration of mammary gland extracts will generally stop profuse menstruation, especially in young girls, and will also many times postpone to normal a too frequent menstrual cycle . . . it is quite probable that the uterus involutes more rapidly and better when the woman suckles her child, possibly from the stimulation of the child at the breast, and as clinically demonstrated, the administration of mammary extracts will generally, if the cause is not pathologic, stop profuse menstruation. The only use for extracts of the mammary gland is in the profuse menstruation of young girls and young women, and in menorrhagia occurring at the time of the menopause; in other words, in functional bleeding."

Another later confirmatory reference may be translated from a treatise on gynecology by Vignes [13] of Paris:

"Some authors suggest that an internal mammary secretion may exist, and it is chiefly upon the results of mammary therapy that this hypothesis is based. Organotherapy with mammary gland extracts has been used by a good number of physicians since 1894. Some of them have no faith at all in its efficacy, while others praise it loudly; for example, Batuaud, one of the first in France to have recourse to it, said: 'In a general way it may be stated that mammary organotherapy is indicated whenever there is premature occurrence of menstruation, a flow that is too profuse or too prolonged, or intercalary uterine hemorrhage, a fortiori when several of these pathologic conditions are combined in the same patient. . . . In about one-twentieth of the

cases, mammary organotherapy is entirely inactive, but in the other nineteen-twentieths its effects are considerable and sometimes rapid.' "

Most investigators believe that lactation amenorrhea is due to hormone action. Candela [14] thinks that the mammary glands produce a hormone that inhibits the ovarian functions either directly or through the antepituitary. For many years mammary extracts have been used empirically to control excessive bleeding thought to be due to ovarian overactivity or ovarian irritability. Clinically, the results have been quite satisfactory. For instance, Cherry [15] states:

"Upon this conjectural and apparently physiologic basis, mammary gland extracts have been successfully used clinically for a number of years in patients suffering from different types of profuse menstrual bleeding."

Chalomen

FOR a number of years a preparation known as Mamma-Pituitary Co. (Harrower) was available as a means of checking abnormal menstruation and pelvic congestion. This was a combination of mammary and pituitary extracts with a small dose of ergotin to sensitize the uterus to the synergistic ingredients. With the development of the two aforementioned antiovarian principles from the corpus luteum and the antepituitary, it was possible to improve this formula. So in 1932 Endoluteum was added, together with a luteinizing fraction from the anterior pituitary (each dose containing an amount which, when administered only once, will luteinize the ovaries in a mature rabbit). At the same time the name was changed to Chalomen since the formula contained the three chalones of menstruation. (See page 81.)

Chalomen is a convenient means of controlling early functional menorrhagia, as it offers a combination of the glands known to oppose menstruation. Besides being used for its antihemorrhagic value, it is employed for its decongestive effects in pelvic congestion, also in utero-ovarian irritability with local discomfort, pain, and, occasionally, erethism. It has been used in fibroids but does not, of course, replace surgery when indicated in the menorrhagia due to uterine neoplasms.

The usual dosage procedure is as follows: One tablet of Chalomen is given at meals and at bedtime; before the onset of the menses this is doubled and continued until the flow is controlled. After a rest of one week, the same procedure is repeated, perhaps several times. Chalomen is not available for injection. Where injections are desirable, give Endoluteum (page 80) or the chorionic gonadotropic (A.P.L.) hormone, APestrin (page 72).

1. Hisaw, F. L., et al.: Proc. Soc. Exp. Biol. and Med., June, 1928, xxv, 754.
2. Corner, G. W., and Allen, W. M: Am. Jour. Physiol., March, 1929, lxxviii, 326.
3. Corner, G. W.: J.A.M.A., May 25, 1935, civ, 1899.
4. Fluhmann, C. F.: California and West. Med., Oct., 1931, xxxv, 279.
5. Smith, G. V. S., and Smith, O. W.: J.A.M.A., Dec. 19, 1931, xcvii, 1857.
6. Kurzrok, Raphael: Endocrines in Obstetrics and Gynecology, page 64. (See Appendix.)

7. Loewenberg, S. A.: Clinical Endocrinology, 1937, page 609.
8. Macht, D. I., et al.: Am. Jour. Physiol., Feb., 1929, lxxxviii, 65.
9. Macht, D. I., and Stickels, A. E.: Proc. Soc. Exper. Biol. and Med., May, 1931, xxviii, 801.
10. Patel, J. S.: Quart. Jour. Exper. Physiol., Oct. 9, 1930, xx, 245.
11. Collip, J. B.: Internat. Clin., Dec., 1932, iv, 51.
12. Osborne, Oliver T.: Principles of Therapeutics, 1921, pages 486, 488.
13. Vignes, Henri: Physiologie gynecologique et medecine des femmes, 1929, page 517.
14. Candela, N.: Arch. di ostet. e ginec., March, 1930, xvii, 97.
15. Cherry, T. H.: Jour. Lab. and Clin. Med., April, 1937, xxii, 711.

LUTEAL—CLINICAL EXCERPTS

Abortion, Habitual.—The use of progestin in habitual and threatened spontaneous abortion is logical and valuable. . . . Thirty-four of the forty-one cases of threatened and habitual abortion were treated successfully with the corpus luteum hormone progestin.—F. H. Falls et al., J.A.M.A., Jan. 25, 1936, cvi, 271.

Abortion, Habitual.—Treatment of these cases with progestin during this critical period should serve to preserve the decidua and inhibit the motility of the uterine muscle, so that the pregnancy is maintained until after the third month when the placenta is fully developed.—P. M. F. Bishop et al., Lancet, Jan. 19, 1935, ccxxviii, 139.

Abortion, Habitual.—It is known for certain that the corpus luteum hormone is necessary for the normal maintenance and development and modification of the endometrium and for the nidation of the ovum until such a time as the placenta is sufficiently developed to be able to function as an independent organ. After this has been achieved the destruction of corpus luteum no longer leads to a termination of pregnancy. Before this event, however, its elimination will lead to abortion. The artificial administration of corpus luteum hormone is capable of preserving pregnancy during this critical period. . . . Threatened abortion due to trauma may also be successfully averted by means of luteal hormone, since apart from its specific action on the endometrium the corpus luteum hormone also inhibits the contraction of the uterine musculature.—C. Clauberg, Practitioner, May, 1937, cxxxviii, 634.

Abortion, Threatened.—It is believed that the action [of placental extracts] is not directly on the ovary but on the pituitary, which in turn stimulates the ovary to form a mature corpus luteum. The latter is the agent necessary to keep the uterus quiet and prevent too great a contraction. From the work of Novak and Reynolds, Morgan, Knaus and others, one may safely conclude that estrin (follicular hormone) acts as the augmentor and corpus luteum hormone as the inhibitor of these contractions.—M. K. Hertz, Med. Rec., Nov. 16, 1938, cxlviii, 372.

Abortion, Threatened.—Corpus luteum hormone has a wide field of usefulness in controlling habitual and threatened abortion and premature separation of the placenta. Progestin may prove useful in central placenta previa and in premature rupture of the membranes to delay labor until the fetus is viable.—F. H. Falls, South. Med. Jour., May, 1938, xxxi, 556.

Afterpains.—We have reported observations showing the complete relief of afterpains in 87.1 per cent. of cases by the administration of a single dose (one rabbit unit) of progestin. Normal processes of the puerperium were unaffected.—S. Lubin et al., Am. Jour. Obst. and Gynec., July, 1936, xxxii, 134.

Articular Disorders.—However, they emphasize that the progesterone therapy is not necessarily indicated in all articular disturbances. They only wish to point out that there are patients in whom the anamnesis justifies treatment with progesterone.—J. F. Touw et al., Abstr., Acta med. Scandin., Oct. 21, 1938, xcvi, 501.

Dysmenorrhea.—It is safe to conclude that corporin can be used in selected cases [dysmenorrhea] with excellent relief; and, corporin, like all other medical treatments, will have its absolute failures and its partial and complete successes.—R. E. Campbell et al., Am. Jour. Obst. and Gynec., March, 1936, xxxi, 508.

Dysmenorrhea.—Thus the dysmenorrheic patient with a large, well-developed uterus which exhibits moderate to large contractions, usually obtains complete relief from pain after treatment with progesterone. The patient with the small hypoplastic uterus, which shows little or no contraction, is likely to respond favorably to estrogenic substance. Using these simple criteria for the proper selection of cases, it should be possible completely to relieve a large proportion of the women who regularly suffer from this common and disabling form of pain.—J. E. Lackner et al., Am. Jour. Obst. and Gynec., Aug., 1937, xxxiv, 248.

Lactation.—Administration of extracts of whole sheep's hypophysis to spayed virgin rabbits caused proliferation of the mammary gland and simultaneous lactation, producing in two weeks a condition scarcely distinguishable from that present at the full term of gestation. Previous preparation by action of the corpus luteum was found not to be necessary to this effect.—G. W. Corner, Am. Jour. Physiol., Oct. 1, 1930, xcv, 43.

Menorrhagia.—The luteinizing hormone which stimulates the production of progestin has been administered, with promising results, to nineteen patients whose chief symptom was abnormal flowing.—G. V. Smith et al., J.A.M.A., Dec. 19, 1931, xcvii, 1857.

Menorrhagia.—Clinical results in menorrhagia of glandular origin treated with mammary therapy would indicate that its action upon the ovary was one of restraint in the manufacture of the estrogenic hormone. When applied in a careful and judicious manner, mammary therapy seems to be selective for these conditions.—T. H. Cherry, Jour. Lab. and Clin. Med., April, 1937, xxii, 711.

Toxemia, Pre-Eclamptic.—The results obtained following the administration of progesterone in twelve cases suffering from severe pre-eclamptic symptoms are given. Clinical improvement appears to have been produced in these cases.—J. M. Robson et al., Brit. Med. Jour., Feb. 13, 1937, 311.

HARROWER LUTEAL (ANTIOVARIAN) PRODUCTS

ENDOLUTEUM

Corpus Luteum (Anteestrous) Therapy

Indications: Ovarian Irritability; Tendency to Abortion; Menorrhagia.

Forms Available: (List No. 119) **Endoluteum Tablets**—each 3 gr. contains Corpus Luteum (N.F. VI) gr. 2, equivalent to 10 gr. fresh bovine corpus luteum. (Bottles of 50.)

(No. 119A) **Sol. Endoluteum.** Aqueous—each cc. contains the water-soluble active material from 75 gr. fresh bovine corpus luteum. (Packages of five and 100 1-cc. amp.)

(Nos. 120A, 120S) **Sol. Endoluteum Fortior**—each cc. contains the water-soluble active material from 150 gr. corpus luteum. (Packages of five and 100 1-cc. amp.; also vials of 10 cc.)

Standardization: This water-soluble extract of corpus luteum is biologically tested for its ability to lengthen demonstrably the diestrous period in adult female white rats.

Dose and Administration: Oral: From 1 to 4 tab. q.i.d. Parenteral: 1 cc. daily is the usual dose.

ENDOLUTEUM in OIL (Progestin)
Natural Progestational Hormone

Indications: Amenorrhea and Oligomenorrhea; Sterility; Habitual and Threatened Abortion; Menorrhagia.

Form Available: (List No. 123A) **Endoluteum in Oil**—a solution of the progestational hormone (progestin) secreted by the corpora lutea. (Packages of five 1-cc. amp.)

Standardization: Endoluteum in Oil is standardized in terms of International Units, each of which represents the physiological equivalent of 1 mg. beta-progesterone. Each cc. contains ½ I.U. This is not a synthetic product.

Dose and Administration: Parenteral only: From ½ to 1 I.U. daily or every other day as required. Do not use during first half (follicular phase) of menstrual cycle.

Pluriglandular Luteal Formulas

CHALOMEN (Mamma-Pituitary Co.)
Oral Antiovarian (Inhibitory) Therapy

Indications: Ovarian Irritability and Utero-Ovarian Congestion; Hyperovarism; Erethism; Menorrhagia; Metrorrhagia; Climacteric Uterine Hemorrhage.

Form Available: (List No. 40) **Chalomen Tablets** (or Capsules)—each 5½ gr. contains Endoluteum (Corpus Luteum—N.F. VI) gr. 1; Mammary Substance gr. 3; Luteinizing Hormone (pituitary) gr. 1/40; Ergotin (Bonjean) gr. ½; Calcisalin (excipient) q.s. (Bottles of 100.)

Dose and Administration: Oral only: 1 tab. (or cap.) q.i.d.; prior to onset of menses and during entire flow give 2 q.i.d.; omit for one week. Repeat cyclic dosage to effect and preferably for at least two periods after flow is normal. Where injections are desirable give **APestrin**, from 100 to 500 rat units daily, during heaviest flow; or **Sol. Endoluteum**, 1 cc. daily, if more suited to circumstances.

PLACENTO-LUTEUM
Parenteral Placental-Luteal Extract

Indications: Toxemias of Early Pregnancy; Tendency to Abortion.

Form Available: (List No. 49A) **Sol. Placento-Luteum**—each cc. contains the water-soluble active materials from 20 gr. fresh glands in the proportions: Placenta 3, Corpus Luteum 1. (Packages of five 1-cc. amp.)

Dose and Administration: Parenteral only: 1 cc. twice daily for several days, especially prior to expected difficulty. May be alternated with **Endoluteum in Oil**, and supplemented with **Endoluteum Tablets**, 2 q.i.d.

VIII.—PITUITARY THERAPY

ANATOMICALLY the pituitary consists of three divisions—anterior lobe, posterior lobe including the pars nervosa, and the pars intermedia. Physiologically this remarkable gland has been described as the "leader of the endocrine orchestra." So far eleven different hormones have been separated from it, or, more accurately, eleven different hormone effects have been demonstrated. Only a few of these principles are as yet available.

The antepituitary is essential to life, and many of the more spectacular pituitary functions are performed by this portion of the gland. It is chiefly concerned with:

1. Control and regulation of skeletal growth.
2. Growth of the gonads and development of secondary sex characteristics.
3. Regulation of the sexual cycle and reproduction.
4. Carbohydrate metabolism.

The posterior pituitary exerts its influence chiefly upon:

1. Carbohydrate metabolism.
2. Peristalsis; involuntary and unstriped muscle contraction; uterine contraction.
3. Renal secretion.
4. Blood-pressure and body temperature.

The proper functioning of nearly all the glands of internal secretion seems to depend on normal pituitary activity. As Winterton [1] puts it:

"The whole endocrine system is controlled by the anterior lobe of the pituitary, which produces hormones that regulate the gonads, thyroid, suprarenals, pancreas, and mammary glands, and governs the growth of the skeleton."

The exact nature of this control is not clearly understood. That there can be a distinct hormone for every function seems incredible to some, and Smith [2] exclaims:

"That this small gland, which in man averages less than 0.5 Gm. in weight, secretes this number of hormones as separate entities throughout the entire secretory process taxes the imagination."

Sir Walter Langdon-Brown [3] suggests that the pituitary gland may be capable of

". . . receiving the impulses from the diencephalon, and producing an activating and an inhibitory hormone of a protein character according to demand, which can speed up or inhibit the secretion of the simpler grade of hormone in the other endocrine glands."

Results of Pituitary Dysfunction

SOME degree of hypopituitarism (anterior lobe) may be the chief etiologic factor in growth dystrophies (shortness of stature), genital infantilism, aberrations in the sexual cycle, and obesity. Among the disease entities based upon antepituitary insufficiency are: infantilism, mongolism, dwarfism, Frohlich's syndrome, Simmonds' disease, Cushing's disease, and the Laurence-Biedl

syndrome. Hypersecretion of the anterior lobe of the pituitary results in gigantism and acromegaly.

Postpituitary hypofunction is considered as a primary etiologic factor in diabetes insipidus, uterine atony, postpartum and other forms of uterine hemorrhage, some types of hypotension, intestinal atony, and obesity (particularly where the serum lipid concentration is upset).

Endocrine disturbances that are probably due essentially to both anterior and posterior pituitary dysfunction, are the Schuller-Christian syndrome, Dercum's disease, and pituitary epilepsy.

Pituitary Feeding and the Pituitary Type of Headache

THE oldest and most inclusive of the pituitary products are pituitary substance and the compound water-soluble extract obtained from the whole gland.

Total extracts tend to amplify the functions of the gland as a whole and are not given for a single-fraction effect. It is probable that pituitary feeding is largely of substitutive and homostimulative value, and that the nature of the response to it varies with the time at which it is given, as well as with the variations in the incretory role of the gland.

The so-called "pituitary headache" is an excellent illustration of the part that the pituitary plays in common endocrine upsets, particularly the menopause. One etiologic theory with many supporters is that pituitary headache is caused by local congestion or actual pressure changes due to the enlargement of the gland within its closely fitting sella turcica. Normally, the pituitary has enough space in this bony cup to allow for physiologic variations in size, but any abnormal enlargement soon produces sufficient pressure to cause headache.

Many cases of pituitary headache are relieved by the oral administration of pituitary substance, apparently because this therapy gives the pituitary an opportunity to "rest and return to normal." The response to such therapy has been considered as a form of diagnostic organotherapy. (See pages 14 and 29.) In some cases, especially in the pituitary headache occurring near the menopause, a pluriglandular formula like Menocrin is clinically more satisfactory. (See page 73.) This basic treatment may be supplemented with a suitable pituitary extract—e.g., Pituitary Co. (Harrower)—by mouth or by injection, or both if desirable. (See page 95.)

Halsey [4] summarizes this subject nicely:

"The frequency with which recurring headache of a peculiar type (bitemporal, very intense, described by the sufferer as 'boring') was present in patients presenting other conditions suggestive of pituitary disturbance, led Pardee to administer pituitary substance to a series of seven such cases. The results obtained were most gratifying; and in all the cases making up this series there was marked amelioration or cure of the headache. The dose employed by Pardee was ¼- to 2-gr. tablets three times a day by mouth. Glassberg reports that the daily administration of 8 gr. of pituitary extract cured severe headache of over two years' duration in a patient presenting various

signs of hypopituitarism. Dalche reports relief of headache from administration of 0.1 Gm. dried extract of the whole gland two to four times daily in a case in which 'an endocrine upset had induced congestion of the pituitary.' Timme and many others have noted that in many cases of dyspituitarism relief of headache followed pituitary medication."

Pituitary Co. (Harrower) was devised to retain the value of a total extract and at the same time accentuate the even more desirable influence of the anterior lobe. The product consists of equal parts of total gland and anterior lobe, each tablet (or capsule) representing 13 gr. of fresh gland tissue.

It is a decided advantage to dose pituitary generously, and as many as 4 tablets q.i.d. may be given. The usual dose is 1 tablet at meals and at bedtime for several weeks, twice this amount for a similar period, 3 q.i.d. for another period, etc. This progressively increasing dosage not only facilitates a maximum response, but enables the physician to determine the patient's tolerance. This is important, for many therapeutic failures are attributable directly to insufficient dosage. Others may be due to neglect of the related glandular problems. This point is stressed in the following discussion.

Organotherapy in Developmental Defects

"INSISTENCE on single-gland medication in such cases is a sort of fetishism. In the practical management of these cases, different preparations that may be effective should be used."

This statement applies in many organotherapeutic fields, but it was made by Hoskins [5] in discussing a report on dwarfism. In the treatment of this lesion the fundamental truth of the statement is so clear that one wonders how it can be denied or ignored by a clinician of experience. The dogma that the only scientific approach to an endocrinopathy is to find the single gland responsible and substitute for it, is an oversimplification that has led to many errors in diagnosis and failures in treatment. This is particularly true in developmental defects in children, and the perfection of the growth-stimulating fractions from the pituitary seems to have accentuated this misconception. Growth is a very complex phenomenon and, as Sevringhaus [6] puts it:

"It is now being suggested that growth promotion is not the result of a separate hormone but rather the combined consequence of the several other materials aforementioned [pituitary, thyroid, gonads, etc.]."

Developmental anomalies in children are usually endocrine in origin, and almost invariably they are pluriglandular syndromes. (We have to exclude, of course, certain congenital heart lesions, structural brain changes, osteogenetic imperfections, rickets, etc.) As a natural corollary the preferred treatment of developmental defects in children is pluriglandular, and the most useful products are thyroid and antepituitary. The hypothyroid child is dull, apathetic, stunted, pudgy, and pot-bellied—the true cretin fails to develop in any notable respect. The hypopituitary case, on the other hand, is usually quite bright, but abnormal, particularly as regards somatic and gonadal

growth and development. The mongol appears to be a mixed type, for almost invariably there are clear evidences of both thyroid and pituitary hypofunction. More common than any of these text-book types, however, is thyropituitary deficiency, without clear-cut cretinism, mongolism, or pituitary dwarfism.

There is some evidence to show that advanced endocrinopathies in children are often the direct consequence of glandular dysfunction in the mother, thus emphasizing the importance of endocrine control during pregnancy. For example, in discussing mongoloid children, Barnes [7] says:

"Second to recognizing the fact that incretions, derived from the mother during intrauterine life if defective or deficient, will affect morphogenesis, is the early recognition and treatment of the mongoloid. To the administration of the properly selected gland or glands (and thyroid, pituitary, and thymus in proper doses to meet special needs are the glands to study) we should employ every measure that will assist in improving the subnormal mental and physical condition of the patient."

Cretinism, pituitary dwarfism, mongolism, and other advanced endocrinopathies in childhood are so relatively infrequent and so well described in the endocrine text-books (listed in Section 7 of the Appendix) that we shall not attempt to cover them here.

Practically every physician has among his patients some children with mental or developmental shortcomings that might be greatly improved by suitable endocrine therapy. Since the two glands chiefly involved are the pituitary and the thyroid, combined therapy is likely to be most helpful. There are many references in the literature to the fact that pituitary and thyroid extracts given together are synergistic. There are also a number of reports by those who believe that pituitary is of no value given orally, but it may well be that a number of these negative reports might not have been so gloomy if combined pituitary-thyroid therapy had been used. No less an authority than Sir Walter Langdon-Brown [8] has said:

"It is positively asserted that pituitary extract given by the mouth is useless, but I have seen too many instances of greater improvement under the combined administration of pituitary and thyroid extracts than of the latter by itself to attribute them to mere coincidence."

No one doubts that in selected cases it may be advisable to supplement oral pituitary-thyroid therapy with antepituitary products hypodermically and with other injectable preparations. Yet constant needling, especially in children, certainly should be disapproved by all conscientious clinicians unless it can be shown that such medication is essential. That this is rarely necessary in retarded children was recently confirmed by Jacobsen and Cramer,[9] whose report was accompanied with striking photographs of their cases before and after treatment, lasting from five months to two years. They state:

"Ten cases are reported of children who have received therapy with anterior pituitary extract. These were selected as illustrative of the kind of results that may be obtained in cases of dwarfism, infantilism, hypogonadism, and certain types of obesity when the response to endocrine treatment is favorable. Experience has shown that desiccated thyroid administered in con-

junction with anterior pituitary extract usually produces more rapid improvement than anterior pituitary extract given alone. Patients who have failed to respond when thyroid alone was given have improved rapidly on combined therapy."

Similar results were obtained by Molitch and Poliakoff,[10] who studied several groups of children in regulated environment for a period of six months, with a similar untreated group serving as controls. Forty-three boys between 10 and 17 years of age, all below the minimum in height for their age according to Engelbach's norms, were selected for treatment. No known cause for the shortness of stature could be demonstrated, and it was concluded that the boys probably had some degree of pituitary infantilism:

"From this study it would appear that the oral preparation [of anterior pituitary] is of value and suggests the use of the hypodermic preparation only when medication by mouth has failed to stimulate growth. There were no unfavorable local and systemic reactions to treatment. . . . Anterior pituitary substances, when given concomitantly with thyroid by mouth and by hypodermic, produced better results than thyroid gland substance alone. Anterior pituitary substances given orally appeared slightly less effective than the extract given intramuscularly. The hypodermic preparation is recommended for use when the oral preparation has failed to stimulate growth."

Of course, overenthusiastic claims have been made in some quarters, but unyielding skepticism surely is no more tenable than outright therapeutic credulity. As Lurie [11] said, after having reported two cases that strikingly demonstrated the effects of pituitary extract given by mouth:

". . . one must not carry skepticism to the point of nihilism. Deductions made from experiments carried out in test-tubes do not necessarily negate the validity of clinical results."

Improvement in the types of children mentioned here and the consequent gratification of the parents and family are familiar experiences to physicians who through the years have applied pluriglandular therapy as materialized in the formula, Antero-Pituitary Co. (Harrower). Now called Pediacrin, this balanced antepituitary-thyroid-thymus product has been used in the field of developmentally defective children with increasing clinical satisfaction for more than twenty years.

In the treatment of backward children, the time element is of great importance and, because the extent of the thyroid and pituitary phases of the etiology may not be known, a regimen such as follows has been found to have diagnostic as well as therapeutic value:

Pediacrin, 1 tablet t.i.d. for four out of every five weeks as "background therapy" for six months. After the first two months, add Endothyrin, two ½-gr. tablets a day for two weeks; 3 a day for two weeks; 4 a day for two weeks; 5 a day for two weeks. Omit Endothyrin after two months. During the third two-month period, add Pituitary Co. (Harrower), 1 q.i.d. for the fifth month and 2 q.i.d. for the sixth and final month of the course. When hypogonadism is prominent or when cryptorchidism is present, injections of the gonadotropic hormone, APestrin (see page 72), or Sol. Pituitary Co. (see page 95)

may be added to the oral background therapy with Pediacrin. This injection therapy is given as circumstances may indicate, but preferably during the last two months of the suggested course.

Endocrine Obesity

WHILE it is true that in all cases of obesity the one common cause is a disproportion between energy intake and output, the importance of the endocrine glands, particularly those with a marked influence on metabolism, cannot be discounted. As Douthwaite [12] puts it:

"It is probably true to generalize to the extent of accusing the pituitary gland of producing nearly all grossly fat children, and of the fatness which may arise after childbirth."

It is well known that obesity frequently is seen in association with genital underdevelopment, castration, amenorrhea, hypothyroidism, the menopause, and pituitary disturbances. Injury to the hypothalamus is also accompanied with obesity, and it may be that this is more significant than pituitary disturbance itself, although one must remember their close functional relations.

Classifications of obesity are not entirely satisfactory, but a useful one is put forward by Zondek:[13]

"1. Alimentary obesity (over-feeding obesity), due to exogenous causes: fat distributed diffusely and uniformly over the whole body.

"2. Endocrine obesity, due to endogenous causes: the adipose tissue shows regional predilection. The hormonal glands in question are the thyroid gland, the pituitary body, the sex glands, the pineal body, the islet system of the pancreas, and the adrenal cortex.

"3. Localized accumulation of fat (lipomatosis)."

Some authors frankly doubt the existence of endocrinopathic obesity, but Ward [14] puts forward an argument difficult to avoid:

"But why do not all overfed and underexercised patients grow fat? And why do some light eaters and heavy workers grow fat? There must be an endogenous reason. The endogenous type of obesity also presents a fairly definite clinical picture, such as localized fat about the supraclavicular spaces, breasts, abdomen, hip-girdle, and ankles. The endogenous type has also been classified according to age, namely: (1) infantile obesity due to thyroid deficiency, (2) juvenile obesity due to insufficiency of the posterior lobe of the pituitary gland, and (3) adult obesity due to thyroid, or pituitary or gonad disturbance, or a combination of these. . . . The adrenals are closely concerned with blood-pressure. Blood-pressure is higher in overweights than in others. The pancreas makes insulin, and lack of insulin causes diabetes. Diabetes is a disease of overweights. May we then say that overweight is an expression often of adrenal or pancreatic disease? Perhaps so."

Doubtless the two main types of obesity (exogenous and endogenous) may be related. At least Ward deems it probable that

". . . the exogenous type might become endogenous by the superfluous intake of calories throwing extra work on the organs or glands that control the oxidative processes, the strain eventually resulting in their disease."

In endocrine obesity, there is a typical distribution of fat associated with certain specific endocrine dyscrasias and, because of this, endocrine obesity

is frequently referred to as hypothyroid, hypogonad, hypopituitary, etc. In actual practice, however, it is much more common to find a mixed type. Regarding this, Douthwaite [12] says:

". . . spontaneous endocrine deficiency can rarely be referred with certainty to a monoglandular disease."

Strangely enough, the type of fat distribution most likely to be associated with a uniglandular lesion is not true obesity. The myxedematous deposits in frank hypothyroidism are not really fat, and because these patients usually have poor appetites a marked accumulation of true fat rarely occurs. Werner[15] describes persons with thyroid obesity as being "fat all over." Unlike the girdle obesity of the pituitary type, the head, neck, and extremities are involved and the clavicles may be obscured with pads of tissue. The distal phalanges do not taper as in pituitary obesity but are blunt and stocky. In obesity of this kind, desiccated thyroid is a specific, and many clinicians have found Endothyrin superior to the ordinary desiccation because of its greater freedom from toxicity. (See page 30.) The dosage should be governed by the pulse rate, nervous response, and periodic determinations of the basal metabolic rate.

The obesity of childhood is usually associated with developmental defects, and Pediacrin may be used as background therapy as already outlined. Frohlich's syndrome is essentially obesity associated with sexual infantilism. Genital underdevelopment is present and puberty is delayed in both sexes, while cryptorchidism is frequently present in the male. Although the exact etiology may be doubtful, there is no question that the pituitary and the thyroid are involved. Here again Pediacrin frequently brings about marked improvement. If the hypogonadism is slow in responding to this treatment, it may be supplemented with APestrin (gonadotropic hormone) and Plestrin (estrogenic hormone) in the female, although the reports previously cited [9, 10] indicate that this injection therapy is seldom necessary in children.

It has been said that three-fourths of all cases of endocrine obesity occur in women. Perhaps there is a fallacy in this figure, because more obese women present themselves for purely cosmetic reasons than for the obesity per se. Yet, more than ever before, the clinician is confronted with an increasing number of overweight women who present obesity plus some evidence of gonad hypofunction. Quite a number are in the menopausal age, and as Douthwaite [12] says:

"At the menopause the ovary, pituitary, and thyroid vary in their degree of complicity in individual cases."

There may indeed be a variation in the degree to which these glands are responsible for the syndrome, but there is no question that they are almost invariably involved. Referring to menopausal obesity, Williams [16] says:

"It matters little whether the disappearance of the ovarian tribute acts on the one hand via the thyroid, or the pituitary, or both; or, on the other, by a direct influence on the body cells through the blood stream. The fact remains that coincidentally with the cessation of this side of ovarian activity, the body

temperature falls. It falls gradually, it remains low, often as low as 96° F. for a considerable period, and then tends slowly to rise again. . . . The fact of this lowered body temperature means diminished combustion, and diminished combustion (on the same intake) means an increased storage of fat."

In the outline of the treatment of obesity recommended by Williams [16] in his book, "Obesity," he remarks:

"In the case of the thyroid, its therapeutic association with another gland will often bring about the success which is denied to the thyroid alone. In my experience the most fruitful combination has been thyroid plus pituitary. . . . It is generally agreed among clinicians that the administration of gonadal extracts by the mouth is very seldom followed by satisfactory results. Of the pure extracts, whether of testis or ovary, I think this is true, though I can gladly testify to having obtained considerable satisfaction from the pluriglandular preparations in which these extracts figure, which are supplied according to Dr. Harrower's formulae."

In these cases of pluriglandular dysfunction a valuable treatment is background therapy with a combination of thyroid, pituitary, and ovarian substance, such as Menocrin. The dosage is 1 tablet q.i.d. When menstrual disorders are also present, it is advisable to follow cyclic dosage, thus: If the patient is menstruating or if there is a molimen, prescribe 2 tablets q.i.d., a.c., for ten days before menses (or molimen); omit for ten days at onset of menses; 1 q.i.d. until ten days before menses; repeat. This may be augmented later with courses of Endothyrin or pituitary therapy, or both.

Many clinicians have found that in women with the pituitary-thyroid-ovarian type of obesity, a standard regimen involving Menocrin, Endothyrin, and Pituitary Co. is valuable. To facilitate better cooperation by the patient, a booklet entitled "Weight Reduction" has been written for the physician to pass on to his patients. It contains explanations about diet and other related information. No reference is made in the booklet to the products used or to their origin. The most useful part is the four-color dosage chart which emphasizes the routine changes in the glandular treatment from time to time. These booklets are available gratis on request, but only direct to physicians.

In some persons with marked hypopituitarism, injections of postpituitary (Liq. Pituitarii Post.—Harrower) may be used in addition to other indicated therapy. Blotner [17] showed that in obese persons a fat test meal was followed by a marked rise in serum lipids which did not occur in thin persons. This could be prevented by administration of pituitrin. Apparently antagonism between insulin and pituitrin extends to fat metabolism as well as to carbohydrate metabolism. Engelbach [18] also found that postpituitary has a favorable effect on pituitary obesity. Usually small doses are given at first, which are gradually increased until the intestinal reaction is obtained. Thereafter injections should be given in addition to the routine oral organotherapy, from 5 to 10 international units three times a week, unless there are contraindications to postpituitary.

It must be remembered that merely to reduce the weight of an obese person is not sufficient. The patients must be educated so that they will be

willing to persevere with "the fat prevention habit." In the majority of cases, to be effective, endocrine therapy must be continued for at least several months. While this can gradually be attenuated and discontinued, the diet must be restricted permanently. The patient must realize that resumption of the old eating habits will bring back the original obesity. Nostrums and freak diets should be avoided. Women particularly should be made to understand that obesity is not merely a cosmetic disfigurement but a serious disease with a definite effect on longevity and liability to complications such as cardiac and cardiorenal disease, diabetes mellitus, gall-bladder disease, foot and knee-joint disorders, etc.[19] In overweight patients there is a higher mortality from pneumonia, influenza, heart disease, cirrhosis of the liver, Bright's disease, and apoplexy. There is also a tendency to high blood-pressure. Obesity is, therefore, a serious disease. However, there is much clinical evidence that, when indicated endocrine therapy is given coincidentally with a proper diet, patients with nutritional obesity and associated endocrine defects tend to lose their abnormal appetites (craving for sweets, etc.) and thus to accept the dietary restrictions more willingly.

Products of the Postpituitary

THE manifold effects of posterior pituitary extract include those on the cardiovascular, respiratory, and renal systems; on smooth muscle; on the metabolism; and, of course, on other glandular structures. Most investigators now believe that these hormones are actually secreted by the pars intermedia and that the posterior lobe merely acts as a reservoir.

The Harrower postpituitary product (Liquor Pituitarii Posterii—U.S.P.) is standardized for its oxytocic effect, and each cubic centimeter contains 10 international units. (See Appendix, Section 5.) It has three important clinical applications: (1) in the control of surgical shock; (2) in obstetrics, for its oxytocic effects and to assist in the expulsion of the placenta, as well as to control postpartum hemorrhage; and (3) in diabetes insipidus.

In 1928 Kamm and his coworkers [20] isolated the two chief active principles of the posterior pituitary, vasopressin and oxytocin, naming them pitressin and pitocin. For clinical purposes, however, the U.S.P. extract is still much more widely used, probably because neither the oxytocic nor the vasopressor principle has been prepared free of the other, which causes some overlapping of their physiologic effects. Some reports indicate that pitocin can be used more safely in patients with high blood-pressure or advanced renal disease. On the other hand, Geiling [21] states:

"No significant alterations of blood-pressure or other untoward effects following solution of pituitary intramuscularly have been noted in the obstetric clinic of the Johns Hopkins Hospital and hence its use seems safe in the toxemias of pregnancy. In addition, no clinical advantage resulted from the employment of pitocin. In fact, in the Hopkins clinic stronger contraction of the uterus was elicited with solution of pituitary than with pitocin. Contrary results are reported from other clinics."

In 1925, Temesvary [22] reported that a certain thymus extract, when combined with the postpituitary solution, modified its oxytocic action so that the uterine contractions were less violent and more rhythmic, simulating more closely natural labor. Temesvary believed that such a combination could be administered safely even during the first stage of labor. Several other reports having appeared to confirm this idea, such a combination was first offered in the United States by Harrower in 1930. It was called Pituthymin.

Many workers feel that the thymus-pituitary combination is a safer ecbolic than postpituitary solution alone. Reports by Der Brucke [23] and also by Kottmeier [24] parallel those of Ham,[25] who, in a report on the use of a pituitary-thymus product in four hundred cases of primary uterine inertia, says:

"This ecbolic produces strong, prolonged and rhythmic labor pains. Uterine tetanus, such as commonly follows the administration of pure pituitary extract, was not noted. No fetal deaths in asphyxia nor any ruptured uteri as a result of thymophysin injections were observed."

On the other hand, less favorable conclusions have been published. Roques and MacLeod [26] believe that the combination is relatively harmless and that it is effective in some cases, but attribute its action to the postpituitary content. Overemphasizing the safety of this product, as compared with Liquor Pituitarii, has given rise to its incautious use by some clinicians. However, a pituitary-thymus combination such as Pituthymin, when used judiciously, certainly has no more deleterious effects than posterior pituitary, and there is enough evidence of its advantages to justify its continued use by competent observers under proper conditions.

Posterior pituitary powder by mouth and injections of the oxytocic solution (already mentioned) are used for their uterine effects largely in the treatment of postpartum hemorrhage and to bring about spontaneous completion in cases of abortion. In some clinics intranasal applications are used for the induction of labor and in primary or secondary inertia. Some clinicians use pituitary solution immediately after the birth of the child to hasten separation of the placenta and to decrease the bleeding during the third stage. This procedure, however, occasionally produces hour-glass contractions of the uterus and necessitates manual removal of the placenta. No hard and fast rule can be laid down, but postpituitary products always should be used with caution during pregnancy, and, except in the treatment of postpartum hemorrhage, should be given in repeated moderate doses rather than in large single ones.

Other Uses for Postpituitary Extracts

THE effect of the postpituitary solution on the serum lipid concentration is mentioned in the section on obesity. Some workers have postulated a separate hormone, lipoitrin, presumably elaborated by the posterior lobe. Postpituitary preparations are used also to overcome the effects of insulin overdosage, since the two substances are antagonistic. Because of its stimulating action on the intestinal musculature, Liquor Pituitarii is frequently

employed to allay postoperative abdominal distension. It also promptly controls the polyuria of diabetes insipidus.

Several workers abroad have reported good clinical results in the treatment of peptic ulcer with postpituitary extract. While small doses of this solution actually increase the gastric and intestinal secretions, Dodds and his coworkers [27] showed that in experimental animals large doses prevented the secretion of gastric juice even in response to histamine stimulation. Recently Metz and Lackey [28] in this country noticed that one of their patients with diabetes insipidus, who also had chronic duodenal ulcer, obtained relief from the latter under postpituitary therapy for the polyuria. They also observed that several other patients with peptic ulcer had moderate polyuria and nocturia, with quite a large volume of night urine and little variation in its specific gravity. On these grounds they studied a number of cases of peptic ulcer, using as treatment only postpituitary extract and a restriction of the coarse, indigestible foods. The dosage was from 15 to 30 international units (equivalent to 1½ to 3 cc. Liquor Pituitarii Posterii—Harrower) daily in divided doses for from seven to fourteen days. Some patients were given from 120 to 160 mg. of posterior pituitary powder daily (40 mg. four times daily thirty minutes after meals and at bedtime) by nasal insufflation. Results have been very satisfactory, although it would be premature at present to attempt an evaluation of this new approach to ulcer therapy.

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PITUITARY—CLINICAL EXCERPTS

Alopecia.—It is quite probable that the patient's alopecia is on an endocrine basis. Besides thyroid activity, investigations of other endocrine glands should be made. Anterior and posterior pituitary substance may be given by injection and by mouth.—Queries and Notes, J.A.M.A., Aug. 13, 1938, cxi, 644.

Diabetes Insipidus.—The polyuria of diabetes insipidus, in the great majority of cases, can be controlled by injections of pituitary extract or pitressin.—O. Leyton, Brit. Med. Jour., Nov. 21, 1936, 1041.

Enuresis.—Pituitary imbalance has also been suggested as a cause of enuresis, mainly because the use of pituitary extract has been strikingly effective in securing control over bladder function. It is administered in doses of 1 to 3 grains three times a day, over a period of weeks or months, reducing the dose when headaches become annoying.—William Wolf (Book, see Appendix) page 643.

Epilepsy.—Besides the diet and the luminal, pituitary therapy has been generally added. The theoretical importance of an adequate pituitary secretion on cortical irritability has been already mentioned. Numerous writers in addition to Tucker have found it a useful therapy. Our present finding that metabolism is often below the normal in these patients is possibly a further indication. The dosage has usually been 2 gr. of the whole gland two or three times a day.—T. K. Davis, Jour. Nerv. and Ment. Dis., Sept., 1929, lxx, 264.

Epilepsy.—Deficiency of the pituitary resulting in epileptic states is an established clinical fact. Any lesion perverting or causing a diminution of the secretion of this gland, or preventing it from entering the third ventricle through the infundibulum will eventually induce states of epilepsy.—J. H. Leiner, New York Med. Jour., July 6, 1921, cxiv, 16.

Epilepsy.—The pituitary seems to have some relationship to epilepsy, there being "a frequent accompaniment of clinical conditions (epilepsy) in which an insufficiency of the pituitary is manifest." (Cushing.) Enlargement of the sella turcica has been noted eight times as frequently in a group of epileptics as in a similar group of normal individuals. When symptoms of pituitary underfunction are manifest, 2 grains of whole pituitary extract given three times a day, has been found effective in controlling the seizures.—William Wolf (Book, see Appendix) page 646.

Frohlich's Syndrome, Pituitary Dwarfism.—In the Frohlich type of dystrophia adiposogenitalis (or the pre-adolescent form) advice is often sought in regard to some of the cardinal features of the disease, such as stunted growth, sexual infantilism, delayed puberty, amenorrhea, etc. If these conditions are caused primarily by reason of insufficient anterior pituitary secretion good results are obtained by pituitary feeding either by itself or in combination with thyroid. In pituitary dwarfism in which skeletal growth was arrested at an earlier age than normal puberty and the epiphyses are still ununited, anterior pituitary feeding will frequently cause a renewal of skeletal growth

even after cessation for a number of years. . . . In other cases the same effect upon growth was produced by feeding anterior lobe alone.—H. G. Beck, Endocrinology, May-June, 1925, x, 327.

Growth Defects.—Thirty-two boys, below the minimum in height for their age, were divided into 3 groups and treated for 6 months. Group A received thyroid alone, group B received thyroid plus anterior pituitary substance by mouth, group C received thyroid plus an A.P.E. intramuscularly. Eleven additional boys were not treated, but served as a control group. The "treated" children had a greater increment in height than the control cases. . . . Anterior pituitary substances, when given concomitantly with thyroid by mouth and by hypodermic, produced better results than thyroid gland substance alone. Anterior pituitary substance given orally appeared slightly less effective than the extract given intramuscularly. The hypodermic preparation is recommended for use when the oral preparation has failed to stimulate growth.—M. Molitch et al., Endocrinology, April, 1938, xxii, 422.

Hypopituitarism.—In pituitary disorders there is often, in addition to the direct lack of pituitary secretion, a failure of the thyroid and ovary. Pituitary preparations in the form of desiccated whole pituitary substance (60 grains, or 4 Gm., a day) or one of the injectable preparations containing the essential anterior pituitary principles (100 units daily) are used. These preparations are often not effective alone. In such instances small doses of desiccated thyroid, an estrogen or gonadotropic substance may be necessary as supplemental therapy.—J. C. Burch et al., J.A.M.A., Dec. 4, 1937, cix, 1869.

Hypopituitarism.—At present we can say that lack of the growth hormone may so shorten the life cycle that old age comes on before adult years are reached, or may merely produce a dwarf. If the sex hormone is also deficient, infantilism of some type results. If the hypothalamic post-pituitary apparatus is also involved there will be obesity and perhaps diabetes insipidus. But the permutations and combinations of these syndromes seem almost endless.—W. Langdon-Brown, Brit. Med. Jour., Nov. 14, 1936, 984.

Hypovarism.—It is customary to fortify this treatment [ovarian] with the simultaneous oral administration of small doses of thyroid extract (1/10 to ¼ grain three times a day) combined with anterior pituitary substance in doses of 3 to 10 grains three times a day, a.c. While it is true that in cases of hypo-ovarism the ovaries may be principally deficient, still experience shows that the combined action is generally crowned with greater success than estrin therapy alone. In fact the estrogenic hormone alone is of little value in primary amenorrhea since it serves to inhibit the anterior pituitary. It is the latter which governs menstruation and which, therefore, should be given at first. But it must be remembered that the anterior pituitary gonadotropic factor should not be given when the ovaries are incapable of function or have been removed.—William Wolf (Book, see Appendix) page 154.

Obesity.—In the discussion of hypopituitarism of the postadolescent group, definite cases will be described which will tend to prove the inefficacy of simple pituitary therapy, as compared with a polyglandular therapy directed toward the thyroid, the adrenals, and the pituitary gland. That is, pituitary extract alone failed to produce any change in symptoms in these cases, while pituitary, thyroid, and ovarian extracts, produced very marked amelioration of all constitutional symptoms.—W. Engelbach et al., Tice's Practice of Medicine, 1921, Vol. VIII, page 467.

Obesity.—In Frohlich's syndrome the functions of both lobes must be interfered with. . . . We can therefore understand why the subject of hypopituitarism becomes obese, for the tissue fat cannot be properly metabolized.

And, as we know, this fat tends to accumulate, particularly round the limb girdles. From the close association between the gonads and the pituitary, we can understand why castration or gonadal defects lead to obesity.—W. Langdon-Brown, Clin. Jour., June 4, 1930, lix, 265.

Obesity.—It is known today to a certainty that the hypophysis, the thyroid, the adrenals, the gonads, and to a certain extent also the pancreas, singly or in combination, play a role in that form of disturbed metabolism which leads to the development of obesity. . . . —M. Kern, Arch. Physical Therapy, Aug., 1930, xi, 418.

Peptic Ulcer.—It has previously been shown . . . that it is possible to prepare an extract of the posterior lobe of the pituitary gland which when injected subcutaneously into animals will produce an acute haemorrhagic lesion of the acid-bearing area of the stomach. . . . It seems justifiable to consider the possibility of a hormonal connexion between the posterior lobe of the pituitary gland, the stomach, and the blood picture.—E. C. Dodds et al., Lancet, May 11, 1935, ccxxviii, 1099.

Peptic Ulcer.—Forty-two individuals with peptic ulcers have been treated with posterior pituitary preparations with satisfactory clinical results in forty. The duration of treatment averaged twenty-eight days, but subjective improvement was present after one to eight days.—M. H. Metz and R. W. Lackey, Texas State Jour. Med., July, 1938, xxxiv, 214.

Pituitary Headache.—Many clinicians report good results [in pituitary headache] with either anterior or posterior gland therapy, by either oral administration or subcuticular injection. The subjects treated have responded best to posterior gland therapy. Both oral and subcutaneous methods have been employed.—W. M. Skipp, Endocrinology, Sept.-Oct., 1934, xviii, 596.

HARROWER PITUITARY PRODUCTS

PITUITARY CO. (Harrower)
A Compound Extract of Pituitary Gland

Indications: Hypopituitarism; Infantilism; Pituitary Obesity.*

Forms Available: (List No. 47) **Pituitary Co. Tablets**—each 5 gr. contains equal parts (gr. 1 1/12) Total Pituitary (N.F. VI) and Anterior Pituitary (N.F. VI), representing a total of 13 gr. fresh glandular material; Calcisalin (excipient) q.s. (Bottles of 100.)

(Nos. 47A, 47 S) **Sol. Pituitary Co.**—each cc. contains the water-soluble active constituents of approximately 18 gr. fresh anterior lobe and 1½ gr. posterior lobe (in natural association, i.e., equal parts of anterior lobe and total gland). (Packages of five 1-cc. amp.; also vials of 10 cc.)

Dose and Administration: Oral: 1 or 2 tab. or more q.i.d., at meals and at bedtime for long periods. Parenteral: 1 or 2 cc. daily, p.r.n., preferably intramuscularly.

***Note:** A booklet explaining dietetic and other matters involved in the treatment of obesity, with dosage chart, suitable for patients will be sent gratis to physicians only. (State how many desired.)

LIQUOR PITUITARII POSTERII (U. S. P.)
Oxytocic Postpituitary Extract (Obstetrical)

Indications: Uterine Inertia; Postoperative Intestinal Stasis; Hemorrhage; Shock; Diabetes Insipidus; Obesity.

Form Available: (List No. 133A) **Liq. Pituitarii Post.**—each cc. contains 10 International Units of the oxytocic postpituitary principle. (Packages of five and 100 1-cc. amp.)

Standardization: One cc. produces an activity upon the isolated uterus of the virgin guinea-pig corresponding to not less than 80 per cent. nor more than 120 per cent. of that produced by 0.005 Gm. of the Standard Powdered Posterior Pituitary prepared as directed in U.S.P. XI, p. 217.

Dose and Administration: Parenteral only: In labor, from ½ to 1 cc. p.r.n. In diabetes insipidus, from 1 to 2 cc. daily. In obstipation and postoperative flatulence, from ½ to 1 cc. every three hours to effect.

Pluriglandular Pituitary Products

PEDIACRIN (Antero-Pituitary Co.)
Antepituitary Therapy with Endothyrin and Thymus

Indications: Backward Children (Growth and Developmental Anomalies); Cretinism; Mongolism.

Form Available: (List No. 2) **Pediacrin Tablets** (or Capsules)—each 5 gr. contains Anterior Pituitary (N.F. VI) gr. 2; Thymus Substance gr. 1; Endothyrin gr. 1/12; Calcisalin (excipient) q.s. (Bottles of 100.)

Dose and Administration: Oral only: 1 tab. (or cap.) twice daily with food for four out of every five weeks for six months. (For children over four years, 1 t.i.d.) If injections are desirable, use **Sol. APestrin** (see page 72) ½ cc. daily or every third day, especially in infantilism and cryptorchidism.

ACCRETIN
A Growth-Stimulating Preparation

Indications: Hypopituitarism; Shortness of Stature; Infantilism; etc.

Form Available: (List No. 156) **Accretin Capsules**—each 5 gr. contains Pituitary (anterior lobe) N.F. VI gr. 2½; Thymus Substance gr. 1½; Vitamin B_1 20 International Units. (Bottles of 40.)

Standardization: Accretin is not standardized in units. Its oral administration accelerates the growth rates of immature animals.

Dose and Administration: Oral only: 1 or more cap. t.i.d., at meals, for several months. Used chiefly to supplement **Pediacrin** (above).

PITUTHYMIN
Postpituitary Oxytocic Extract and Thymus

Indications: Uterine Inertia in Labor, etc.

Forms Available: (List Nos. 155A, 155S) **Sol. Pituthymin**—each cc. contains 10 International Units of the oxytocic principle with the water-soluble active principles of thymus. (Packages of five 1-cc. amp.; also vials of 10 cc.)

GERANTIN (Gonad Co.)
Antepituitary, Thyroid, Adrenal, Gonad

Indications: Hypogonadism; Hypopituitarism; Eunuchoidism; Impotence; etc. (See page 106.)

MENOCRIN (Thyro-Ovarian Co.)
Antepituitary, Thyroid, Ovary

Indications: Menstrual and Menopausal Disorders. (See page 73.)

GOVARIN (Gonad-Ovarian Co.)
Menocrin, Antepituitary, Orchic

Indications: Hypovarism; Hypopituitarism; Utero-Ovarian Hypoplasia; Menstrual and Sexual Insufficiency. (See page 74.)

IX.—MALE GONAD THERAPY

IN 1889 one of the most famous physiologists of his day, Brown-Sequard[1] of Paris, published some arresting personal experiences with testicular therapy. Of the effects thus produced, the most remarkable was his increased capacity for work in the laboratory of the College de France. Unfortunately, the enthusiastic use and abuse of Brown-Sequard's conclusions by the charlatans of France soon threw the whole subject of male gonad therapy into scientific disrepute. It is only within the last decade that the male sex hormones, having been physiologically standardized, and more recently one of them having been produced synthetically, have gained the respect and attention of the entire medical profession.

The Male Sex Hormones

LYDIN, a natural male sex hormone, was first made available by Harrower as a standardized aqueous extract of bovine testes in 1927. As later research showed the active substance to be more soluble in fat than in water, a thin vegetable oil was used as a vehicle for the male sex hormones. Lydin is made from ox testes and in this respect differs from the synthetic testosterone, which is usually prepared from sterols extracted from soy-beans. (See Appendix, Section 2.)

The activity of Lydin is demonstrated by its ability to cause regeneration of the seminal vesicles, Cowper's gland, prostate, and vas deferens in castrated rats, and to stimulate the comb growth of capons. In addition to its effect on the accessory sex organs, Lydin has a definite tonic action which usually is manifested by an increased sense of well-being and vigor, especially in elderly persons, much as Brown-Sequard reported in his epoch-making announcement.[1]

The comb-growth effect provides a useful method of standardization, and Lydin contains 2 capon units per cubic centimeter according to the method of Gallagher and Koch.[2] McGee[3] was perhaps the first to isolate this active lipid fraction, which has been described under several different names. It is probably identical with androstenedione, isolated by Ogata and Hirano.[4] McCullagh and his associates[5] have described it as follows:

"The testes produce a substance called androtin, which causes comb growth in the caponized roosters, and which is responsible for the development and maintenance of most of the unique attributes of the male."

Developments with the androgens emphasize similarities between them and the estrogens. Their administration raises the male sex hormone levels in the blood-serum and urine in hypogonadism, just as the estrogens increase the female sex hormone levels. Experimental work seems to confirm the statements of Moore and his coworkers[6] in the University of Chicago, that these effects are exclusively supplementary—that the androgens and estrogens are useful for replacement therapy only.

Lydin is indicated in sexual debility, lack of libido, erectile weakness, impotence, premature senility, delayed puberty, and benign prostatic hypertrophy. Because the male sex hormone does not affect the other glands that regulate gonad function and does little to reestablish gonad activity in the majority of cases, Lydin is most effectively and rationally used in combination with Gerantin (formerly Gonad Co.) by mouth. This Harrower formula is a combination of orchic concentrate with extracts of prostate, adrenal cortex, pituitary, and thyroid. In cases of true aspermia and male sterility, Lydin is probably not so effective as the anterior pituitary-like gonadotropic hormone, APestrin. (See page 72.)

The production of crystalline androgenic extracts (androsterone from urine, and testosterone from testes) led to the synthesis of testosterone by Ruzicka [7] and later to the preparation of a propionic acid ester of testosterone by Miescher and his coworkers.[8] This material definitely raises the androgen level of the blood and urine, and brings symptomatic benefits in various manifestations of senility and gonad insufficiency, such as have been mentioned above.

Its origin (from the humble soy-bean) has permitted an increase in its concentration as well as a reduction in its cost. The potency of the crystallized hormone extracted from urine is very high—according to Wolf,[9] 0.001 mg. is equal to one bird unit. Thus 5 mg. would equal approximately 5,000 such units. The Harrower product known as Testocrin is offered in a thin oily solution containing 10 mg. of the salt per cubic centimeter. The dose is from 1 to 2 cc. three times weekly.

The differences between the natural male sex hormone, Lydin, and synthetic testosterone are not definitely understood. It may well be that the testes produce two or more hormones, so that the various androgenic substances at present isolated constitute fractions of the androgenic complex.[10] Comparisons between the therapeutic merits of the natural lipid extract, Lydin, and the synthetic Testocrin are extremely difficult, but both have demonstrable merit. Whichever of these substances is used, it is, we believe, an advantage in many cases to combine male sex hormone therapy with pluriglandular support of the gonad-regulating glands, as with Gerantin.

Misunderstandings about Male Gonad Therapy

MANY failures in sex hormone therapy, both male and female, may be attributed to "single-gland fetishism" (see page 84), and a tendency to oversimplify the issue by thinking of the ovaries and the testes as independent, self-propelling mechanisms in full control of all the sexual functions. That such a misconception should exist in the face of our knowledge of the striking effects of certain antepituitary, thyroid, and adrenal cortex lesions on sexuality, is indeed strange. However, it is disappearing as the glandular interrelationships are being better understood.

A striking example of hypogonadism with non-testicular etiology was

reported recently by McCullagh.[11] A man 50 years of age complained of increasing impotence and loss of sexual libido over a period of eighteen months. Assays for urinary androgens repeatedly showed low values. When the patient was given a male sex hormone product, some improvement was noted and the urinary androgens rose to comparatively normal. As soon as the therapy (testosterone) was discontinued, the urinary androgens fell to a low level and the impotence recurred. Some time later the patient developed evidences of hypothyroidism, confirmed by the B.M.R. When given thyroid therapy alone without male sex hormone therapy of any kind, there was more marked clinical improvement than following testosterone injections. Not only so, but the thyroid therapy was accompanied with a significant rise in the level of the urinary androgens and disappearance of the impotence.

This case is not cited as an example of a common type of hypogonadism, which indeed it is not, but as an arresting illustration of how closely the testes depend upon related glands and of how thyroid extract may have a better activating effect on gonad function than does the male sex hormone itself. In Chapters III and VIII comment has been made on the synergistic effect of thyroid when given with other gland extracts and its ability to potentiate the functions of other members of the glandular family. For this reason many of the Harrower formulas—Gerantin, for instance—have a small thyroid ingredient, which is particularly important in formulas designed as an indirect pluriglandular approach to the treatment of hypogonadism.

The object of a broad synergistic therapy as with the pluriglandular formula, Gerantin, is to activate the gonad function by "nudging" the gonad-controlling glands as well as the gonads themselves. This is analogous to the use of Menocrin as background therapy in female hypogonadism (Chapter VI). That the glands involved in the gonad-regulating mechanism are as important as the gonads themselves in functional hypogonadism has been emphasized by many workers. Years ago Belfield[12] stated:

"It seems probable that gonad therapy also, begun as an irrational attempt at an impossible 'rejuvenation,' may emerge from the disrepute of its infancy, and develop into a valuable means for relieving ailments that are not now associated with gonad deficiency; for it is demonstrated that the gonad does not originate sex; that it is less essential to the maintenance of sex than is the thyroid or the suprarenal; and that it is indeed one of a chain of interacting endocrine glands, efficiency in every link of which is essential to normal function, sexual or somatic."

To discern the remote etiology of many cases of hypogonadism (and other functional endocrinopathies) is to have a key that unlocks many endocrine enigmas. The role of the antepituitary, for example, is fully as important as that of the gonads themselves. Referring to this, Davis [13] remarks:

"Insufficiency of the anterior lobe of the pituitary body, from any cause, produces an atrophy of the testicle involving all its elements and followed by sterility, impotence, and the constitutional changes associated with genital insufficiency."

Single-gland therapy is often an endocrine version of the common error of the superficial clinician—treating symptoms rather than the disease. Obvious gonad difficulties may be symptoms of less obvious causative endocrine lesions. Lower[14] emphasizes the frequency of this error and indicates the rationale of pluriglandular therapy in hypogonadism thus:

"In spite of an accumulating knowledge regarding the interaction of the hormones produced by the endocrine organs we are still too prone to treat only the gland which is obviously malfunctioning without seeking to discover whether the cause of that malfunction may be some disorder in another related gland . . . in dealing with diseases of the sexual organs it may be that some distant gland is in part at least responsible for the condition."

Gerantin has a wide field of usefulness in the syndrome of the so-called "male climacteric," which, in addition to sexual debility, is usually accompanied with marked mental and physical depletion. In advanced cases of impotence, as well as in hypoplasia and eunuchoidism, it will be necessary, of course, to use supplementary injections of APestrin, Lydin, or similar gonadotropic products. A prominent genito-urinary specialist, Victor G. Vecki,[15] used Gerantin over a period of years, and in his book on "Sexual Impotence" says:

". . . I have found, when studying various cases of sexual impotence, many where the different organic extracts are indicated and frequently give good results. While small doses of thyroid always do some good whenever indicated, pluriglandular preparations sometimes astonish by the effects obtained. In neurasthenic conditions with low blood-pressure, a compound preparation of the adrenal, the thyroid, and gonads very often brings prompt improvement."

The dosage of Gerantin is 1 or 2 tablets (or capsules) q.i.d., a.c. Sometimes it is advisable to give this in graduated dosage, as 1 q.i.d. for two weeks, then 2 q.i.d. for a longer period, followed if necessary by another period with even 3 q.i.d. in conjunction with associated treatment. This formula is available also in solution for parenteral use, the dosage being 1 or 2 cc. daily or every other day for ten days or two weeks of each month, especially during periods of heavy oral dosage of the corresponding formula. (See page 106.)

Prostatic Hypertrophy as a Reaction to Hypogonadism

JUST as the functional integrity of the testes cannot be maintained without adequate thyroid, antepituitary, and cortico-adrenal secretion, so apparently the prostate is dependent upon testicular activity. It seems more and more certain that benign prostatic hypertrophy is a compensatory reaction to waning gonad function. It is on these grounds that the formula, Prostate Co. (Harrower), now called Prostocrin (a combination of prostatic and orchic extracts), has been used with favorable results in this condition since 1920.

Ten years ago, Humphris[16] outlined the rationale of gonad therapy in benign prostatic hypertrophy when he said:

"The fact that prostatic hypertrophy quite commonly follows the functional retirement of the testes has caused many observers to believe that there is some relationship between the endocrine activities of both these

glands. It is believed that when the testes become functionally inactive the prostate becomes enlarged in a compensatory fashion, just as other ductless glands enlarge when closely related glands are put out of commission. It is generally accepted that, when deep-seated infective processes and essential new growths of the prostate gland can be excluded, there remains a form of enlargement of the prostate gland which is closely related to waning gonad function. This should theoretically respond to treatment by organotherapy, which would supplement the endocrine function of the testes and thereby lessen the probable necessity for overactivity of the prostate."

Walker [17] states that Paul of Liverpool was one of the first to suggest that prostatic enlargement was essentially an involutionary lesion similar to that which occurs in the female breast at the menopause. The etiology of prostatic hypertrophy has at various times been considered to be an inflammatory lesion, an adenoma, or a form of degeneration associated with arteriosclerosis; but an increasing number of observers are beginning to regard it as an expression of endocrine imbalance. Sixteen years ago this was an entirely new idea, and Walker[17] quotes from a lecture of his own before the Royal College of Surgeons in 1922. In the light of present knowledge, these words had prophetic value:

"The close dependence of the prostate on the ductless glands, during its period of development, affords sufficient ground for considering carefully the possibility that enlargement may be associated with some change in the endocrine system. The menopause in the female is generally accompanied by a temporary loss of endocrine balance, and it is not improbable that a similar state of affairs may arise during the period of sexual decline in the male. . . . The condition of the endocrine glands in cases of prostatic enlargement offers a fruitful field for research."

Experimental proof of this was offered by Rusch and Kundert,[18] who found that the anatomic and physiologic integrity of the prostate gland in animals is dependent upon stimuli from the gonads. Castration leads to prostatic hypertrophy, while administration of the male sex hormone to a castrated animal maintains the prostate in normal condition.

A number of clinical workers, among them Lower, have obtained favorable results by oral testicular therapy in prostatic hypertrophy. On the basis of Lower's work at the Cleveland Clinic, McCullagh[10] states:

"It has been established that the feeding of desiccated testicular material to patients suffering from benign prostatic hypertrophy will in many instances relieve them of their symptoms."

Van Cappellen[19] has obtained symptomatic relief also from injections of the synthetic testosterone. Using a natural liposoluble testicular extract similar to Lydin, Bergmann[20] found that

"The inhibitory action on the prostate then becomes apparent and relief of the patient is noted in a feeling of well-being, a decrease of nocturia and greater care in voiding, and the complete cessation of perineal pain. . . . It has been noted that to produce the stage of well-being the injections must be given once weekly over a period of time."

Experimentally, Myers and associates[21] observed that the feeding of desiccated testicular substance to adult male rats caused a reduction in the

size of the prostate. Lower and McCullagh[22] repeated and confirmed these experimental results, and in clinical practice obtained relief in 63 per cent. of seventy-six patients with benign prostatic hypertrophy who were treated orally with a desiccation of beef testes. More recently, Cuneo and Jomain [23] compared total gland extracts with the androgenic fractions and found this cruder substance superior. They state:

"We preferred to utilize as our therapeutic agent a total testicular extract rather than a definite substance such as testosterone or androsterone which have been isolated from this extract and recently produced synthetically."

In addition to the favorable influence on functional disorders, particularly pollakiuria, associated with prostatic hypertrophy, these French writers showed that oral testicular therapy modified the physical and roentgenologic signs of the adenoma. They believe that, if treatment is begun early in the course of prostatism, it may have a prophylactic value. Even when the hypertrophy is advanced, favorable results are often produced; and, after endoscopic prostatic resection, relapse may be prevented.

Surgical intervention is necessary, of course, in many cases of prostatic enlargement, but many observers now feel that except in cases of emergency every patient with this lesion should be given the benefit of endocrine therapy before being subjected to surgery.

For twenty years this principle of gonad replacement therapy in benign prostatic hypertrophy has been materialized in the formula, Prostate Co. (Harrower). Now called Prostocrin, this preparation consists of prostate and orchic extract (Leydig cells) āā gr. 2, nucleic acid gr. ¼, excipient q.s. ad gr. vi. The dosage is 4 tablets daily for several months, but it is advantageous to double this dose for short periods. Prostocrin may be alternated with Gerantin (already referred to), and injections of Lydin or Testocrin, 1 cc. daily or every other day, may be used to supplement the oral therapy.

The Treatment of Juvenile Hypogonadism

THE broad value of pituitary-thyroid therapy, as with Pediacrin, in developmental defects in children has been considered in Chapter VIII. In a review of the case histories of 521 boys, Gordon[24] states that hypogonadism and cryptorchidism occur almost twice as frequently in the endocrine as in the non-endocrine group. In this series, thirty-eight boys with cryptorchidism and thirty-six with hypogonadism without cryptorchidism showed a thyroid-pituitary deficiency. Using oral thyroid and pituitary therapy in increasing dosage, Gordon obtained successful results in a high percentage of these cases. In another group he gave injections of anterior pituitary; in still another group, in addition to the thyroid-pituitary feeding, he gave injections of the anterior pituitary-like hormone such as APestrin. (See page 72.) Gordon believes that no boy with hypogonadism or cryptorchidism should be subjected to operation until he has had the benefit of organotherapy for at least six months. Many other authors might be cited, but this

subject has already been fairly adequately covered. It is mentioned here because, in a certain percentage of cases with marked sexual underdevelopment, Lydin may be added to other indicated therapy.

Rejuvenation

THIS term has fallen into ill repute because of its use as a catch word to exploit certain pseudoscientific devices and "cures." Nevertheless, there is every reason to believe that the male climacteric is a reality, that something corresponding to the menopause takes place in men between 45 and 55 years of age, and that something endocrine can be done about it. Virility and endurance beyond this age are definitely related to the gonad function. There are many evidences that the use of products such as Gerantin or Prostocrin by mouth and Lydin by injection, in addition to their effects on the accessory reproductive organs, have a general tonic effect which is manifested by a marked improvement in the patient's outlook and capacity for exertion. Thus, Cuneo and Jomain,[23] whom we have already quoted, state:

"Finally, it seems necessary to emphasize the changes in the general condition of the patient under the influence of the treatment. One is sometimes struck with the veritable rejuvenation of the subject, who at the same time reports increased activity and well-being."

Commenting on Lower and McCullagh's report of their use of testicular extract in benign prostatic hypertrophy, Hutton[25] remarks:

"These preparations will also add zest to the life of the middle-aged. If they do not add years to life, they at least add life to years."

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3. McGee, L. C.: Proc. Inst. Med., 1927, vi, 242.
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18. Rusch, H. P., and Kundert, P. R.: Jour. Urol., Sept., 1937, xxxviii, 316.
19. van Cappellen, D.: Brit. Jour. Urol., March, 1936, viii, 45.
20. Bergmann, V. H.: Jour. Missouri St. Med. Assn., April, 1937, xxxiv, 119.
21. Myers, H. B., et al.: Proc. Soc. Exper. Biol. and Med., May, 1933, xxx, 1099.
22. Lower, W. E., and McCullagh, D. R.: Med. Clin. N. Am., May, 1936, xix, 1949.

23. Cuneo, B., and Jomain, J.: Presse med., June 11, 1938, xlvi, 913.
24. Gordon, M. B.: New York State Jour. Med., Sept. 15, 1936, xxxvi, 1313.
25. Hutton, James H.: Jour. Am. Inst. Homeop., July, 1938, xxxi, 389.

MALE GONADS—CLINICAL EXCERPTS

Eunuchism.—A post-puberal eunuch has been treated with testosterone propionate. Sexual function and libido returned almost immediately. . . . There was an increase in weight of 16 lb. in twelve weeks.—G. L. Foss, Lancet, Dec. 4, 1937, ccxxxiii, 1307.

Eunucheidism.—In every case it is wise to fortify the substitution of the testicular hormone by combining it with those of related glands which are proved or at least strongly suspected to be involved in a given case. The most important of these is the anterior lobe of the pituitary. . . . Orally anterior pituitary substance . . . is helpful. . . . Small doses of thyroid substance are often put into the same capsule.—William Wolf (Book, see Appendix) page 196.

Hypogonadism.—A genitally hypoplastic man . . . was subjected to injections of testosterone propionate . . . [after five months] the genital condition had become improved to such a degree that the patient married, cohabited and ejaculated live spermatozoa. While the voice became somewhat deeper, distribution of hair and the initial beardlessness remained unchanged.—H. S. Rubinstein, J.A.M.A., Nov. 12, 1938, cxi, 1818.

Hypogenitalism.—The use of either androgen or the gonadotropic principle of pregnancy urine in the treatment of hypogenitalism (principally during childhood and adolescence) has been successful in many cases. Treatment of the patient with these preparations is worthy of trial and should extend over a period of at least six months.—Queries and Minor Notes, J.A.M.A., Sept. 24, 1938, cxi, 1235.

Impotence.—The treatment of sexual impotence used to be a rather distressing undertaking until the development of endocrinology and organotherapy. The study of the internal secretions has done for sexual weakness almost as much as antitoxin has done for diphtheria.—Victor G. Vecki, Urol. and Cutan. Rev., Sept., 1926, xxx, 513.

Impotence.—P. J. Reiter (Ugesk. f. Laeger, Aug. 26, 1937, 883) gives an account of eighty cases of impotence in the male observed in the ten-year period from 1927 to 1937. . . . Of the twenty cases receiving hormone treatment seven recovered and five improved. . . . The author concludes that hormone treatment of impotence, though yet in its infancy, is remarkably effective provided the dosage is not too timid.—Abstr., Brit. Med. Jour., Nov. 20, 1937, 78.

Impotence.—. . . certain patients with impotence and low levels of urinary androgens, which we believe are the result of poor general health have not been consistently improved. . . . There is a group of patients with impotence, however, . . . who have testicular deficiency as judged from the low level of urinary androgens, and in this group treatment with testosterone propionate brings about more consistent and more pronounced improvement.—E. P. McCullagh, J.A.M.A., March 18, 1939, cxii, 1044.

Neurasthenia, Sexual.—According to Beard, the sexual nervous exhaustion may be considered as cause, effect, or accessory to the other kinds of neurasthenia, but must, nevertheless, when fully developed, be distinguished from them. . . . Beard considers sexual neurasthenia . . . almost the most important of all the forms of neurasthenia. . . . He further asserts that the clinically connected local conditions of sexual weakness in man, . . . are to be

looked upon merely as symptoms of sexual neurasthenia.—Victor G. Vecki, "Sexual Impotence," 1920, page 126.

Prostatic Hypertrophy.—It has been established that the feeding of desiccated testicular material to patients suffering from benign prostatic hypertrophy will in many instances relieve them of their symptoms.—D. Roy McCullagh, Endocrinology, March, 1939, xxiv, 326.

Prostatic Hypertrophy.—Our knowledge concerning the endocrine influences on prostatic activity indicated that the imbalance might be the result of the failure of the testes to produce adequate quantities of inhibin. Seventy-six cases of benign prostatic hypertrophy have been treated with a testicular preparation and in 63.1 per cent they have been relieved of the symptoms for which they sought medical aid.—W. E. Lower et al., Med. Clin. N. Am., May, 1936, xix, 1949.

Prostatic Hypertrophy.—This condition is connected with and in some way dependent upon a decline in the production of testicular hormones or failure of utilization of the sex hormones of the anterior lobe. . . . Undoubtedly every victim of prostatic hypertrophy, unless he is faced with an emergency operation, should be given the benefit of endocrine therapy before he is subjected to any surgical procedure.—James H. Hutton, Jour. Am. Instit. Homeop., July, 1938, xxxi, 389.

Prostatic Hypertrophy.—The authors employed the testicular extract in the treatment of uncomplicated hypertrophy of the prostate, in cases in which the prostatic hypertrophy was complicated by acute complete retention of the urine and in cases in which the hypertrophy was complicated by prostatitis. They say that testicular extract exerts a favorable influence on the functional disorders that accompany the prostatic hypertrophy, particularly the pollakiuria, and they gained the impression that its prolonged application may modify the physical and radiologic signs of the adenoma. If it is begun at the time of the first appearance of prostatism, it may prove of prophylactic value. However, even in cases of confirmed hypertrophy of the prostate, it may produce favorable results.—B. Cuneo and J. Jomain, Presse med., June 11, 1938, xlvi, 913; Abstr., J.A.M.A., Aug. 6, 1938, cxi, 576.

HARROWER GONAD PRODUCTS

LYDIN (Male Sex Hormone)
A Standardized Natural Male Sex Hormone

Indications: Hypogonadism; Presenility; Asexualism; Impotence; Prostatic Hypertrophy; Eunuchoidism.

Forms Available: (List No. 128A) **Sol. Lydin**—each cc. contains the oil-soluble male sex hormone extracted from bovine testes, standardized to contain 2 capon units per cc. (Packages of five 1-cc. amp.)

(No. 128) **Lydin Capsules**—each soluble elastic capsule is standardized to contain approximately ½ capon unit of the active lipid testicular extract. (Bottles of 40.)

Standardization: Lydin Solution is standardized by measuring its effect upon the growth of the secondary sex tissues (comb and wattles) of capons. The method used is that of Gallagher and Koch. One capon unit is defined as the amount of solution which, injected into a leghorn capon daily for five days, will produce an average of 5 mm. increase in the length × the height of the comb. Each cc. contains 2 capon units.

Dose and Administration: Oral: 1 or 2 cap. q.i.d., at meals and at bedtime. Parenteral: 1 or 2 cc. daily, later every other day. Both forms may be given simultaneously.

TESTOCRIN (Androgenic Hormone)
Synthetic Testosterone

Indications: Male Sex Hormone Deficiencies (Hypogonadism); Low Serum-Androgen Levels; Eunuchoidism; Benign Prostatic Hypertrophy; Impotence; Senility; etc.

Form Available: (List No. 71 S) **Sol. Testocrin**—each cc. contains 10 mg. crystalline testosterone. (Vials of 10 cc.)

Dose and Administration: 1 or 2 cc. daily or twice a day; later 1 cc. weekly. May be supplemented with the oral administration of **Gerantin** (below).

Pluriglandular Gonad Formulas

GERANTIN (Gonad Co.)
A Compound Male Endocrine Tonic

Indications: Hypogonadism; Eunuchoidism; Impotence; Asexualism; Senility.

Forms Available: (List No. 70) **Gerantin Tablets** (or Capsules)—each 5 gr. contains Lydin (page 105) gr. 1½; Prostate Extract gr. 1½; Adrenal Substance (N.F. VI) gr. ½; Anterior Pituitary (N.F. VI) gr. ½; Endothyrin gr. 1/24. (Bottles of 100.)

(Nos. 70A, 70 S) **Sol. Gerantin**—each cc. contains the active water-soluble material from 20 gr. fresh glands in the proportions: Prostate 36, Testes 36, Antepituitary 12, Adrenal (total) 12, Thyroid 4. (Packages of five 1-cc. amp.; also vials of 10 cc.)

Dose and Administration: Oral: 1 or 2 tab. (or cap.) q.i.d., at meals and at bedtime. It may be advisable to give prolonged graduated dosage, as 1 q.i.d. in conjunction with associated treatment with injections of **Lydin** or **APestrin.** (See page 72.) Parenteral: 1 or 2 cc. daily or every other day for ten days or two weeks of each month, especially during periods of heaviest oral dosage of the corresponding formula.

PROSTOCRIN (Prostate Co.)
Endocrine Therapy in Prostatic Hypertrophy

Indications: Hypogonadism; Benign Prostatic Hypertrophy; Senility.

Form Available: (List No. 48) **Prostocrin Tablets**—each 5 gr. contains Prostate Extract (1:6) gr. 2; Orchic Substance (1:9) gr. 2; Nucleic Acid gr. ¼; Calcisalin (excipient) q.s. (Bottles of 100.)

Dose and Administration: Oral only: 1 tab. q.i.d., at meals and at bedtime for several months. Periodic increases are desirable, e.g., double dosage on alternate weeks. May be supplemented with **Lydin** both by mouth and by injection, or with injections of **Sol. Testocrin** (above).

ADREMIN (Adreno-Spermin)
Orchic, Adrenal Cortex, Thyroid

Indications: General Endocrine Tonic Agent. (See page 23.)

GOVARIN (Gonad-Ovarian Co.)
Orchic, Antepituitary, Ovary, Thyroid

Indications: Amenorrhea; Utero-Ovarian Hypoplasia; Infantilism; Sterility. (See page 74.)

PARACALCIN (Para-Spleen Co.)
Orchic, Spleen, Parathyroid

Indications: Chronic Ulcerative Conditions. (See page 111.)

X.—OTHER GLANDULAR PRODUCTS

COMPARED with the pituitary, thyroid, gonads, and other governing glands of internal secretion, the spleen, parathyroids, thymus, pineal, kidneys, stomach, and heart muscle are of minor endocrine importance. Extracts of some of these glands have definite therapeutic value, with a fairly good background of acceptance in the literature. Others are used empirically and their position as therapeutic agents is not unassailable.

SPLEEN.—In 1913 the famous internist, Sir Lauder Brunton, asked the writer to prepare a review of the status of the spleen as a gland of internal secretion and as a source of organotherapeutic agents. This effort was submitted by Sir Lauder to the Editor of the Lancet, who published it.[1]

Early workers considered the spleen chiefly as a key organ in the body's defense system. (This was probably suggested by the enlargement of the spleen which occurs during many infections.) Twenty-five years ago Bayle [2] was using splenic organotherapy in chronic infections like tuberculosis. In spite of the improvement in the treatment of tuberculosis, many modern workers still find spleen extract a valuable adjuvant. Swan,[3] for example, concludes:

"From the observations and results I have obtained in the treatment of tuberculosis with spleen extract, I would conclude that it has a specific effect on this disease."

Part of the action of spleen in tuberculosis may be to promote the utilization of lime. Bayle himself claimed that spleen extract could be made to oppose the tendency toward calcium loss, and research done some years ago under our direction [4] showed that spleen extract is capable of bringing about decisive changes in the blood-calcium level.

Perhaps the most important action of spleen extract in infectious diseases, however, is its ability to stimulate the natural defense forces of the body. Actual histological studies have demonstrated the increased power of the reticulo-endothelial system to take up dyes after spleen therapy. The number and resistance of the leukocytes are decreased following splenectomy in rabbits.[5] By feeding spleen to experimental animals, some Japanese workers [6] were able to demonstrate that the spleen accelerates antibody formation. The mechanism of the action of spleen extract in enhancing immunologic responses is probably similar to that of the non-specific antigens.

Some years ago pupils of von Zumbusch [7] showed that the injection of an albumin-free spleen extract, even in small amounts, diminished the number of eosinophils in dermatoses associated with eosinophilia, and that accompanying pruritus was stopped. A case of generalized desquamative erythrodermia was cured by this method. Von Zumbusch mentions cases of eczema of ten years' standing in which spleen extract corrected the condition after every other treatment had failed. Paul, [8] confirming the German claims, says:

"To state that hives will disappear in fifteen minutes, that the itching and oozing of an eczema will cease in half an hour, and that an eczematous lesion, regardless of its degree of lichenification, will vanish in a few days, as the result of a hypodermic injection, seems preposterous, yet such has been the writer's experience in a series of sixty-one cases."

The Harrower product, Splenocrin, has been used by many clinicians with considerable satisfaction in the treatment of dermatoses and other allergic states associated with eosinophilia.

Another field for spleen therapy has been investigated by Wheeldon,[9] who reports good results in bone and joint tuberculosis, as follows:

"The use of splenic extract in the diet of patients suffering with bone and joint tuberculosis has been found very beneficial, as improvement is noted in the febrile condition, the local reactions, the growth, the weight, the color, the appetite, the blood composition, the deformity, the complications, the roentgen picture, the activity permissible to the patients, and the dispensing with support."

Wheeldon [10] also reports on the use of a spleen extract in forty-five cases of fracture with non-union, in which there were only three failures. He suggests that spleen therapy in these cases probably acts by increasing calcium retention. Here, of course, an oral extract was used.

While the exact mode of action of a product such as Splenocrin cannot be defined clearly as yet, there is a good deal of evidence that spleen extract is an effective organotherapeutic agent in properly selected cases. Splenocrin is a highly concentrated, deproteinized, aqueous extract of spleen, standardized to contain 40 mg. of solids per cubic centimeter. Because of its reticulo-endothelial-stimulating effects, it would seem to be rational therapy in chronic infections and low resistance. There are some remarkable reports concerning its use in certain dermatoses, notably eczema and urticaria.

Heteril.—Heteril is a heterogenetic lipoproteogen. It consists of a lipid-protein complex (Forssman's antigen) derived from the stroma of sheep erythrocytes, in combination with spleen extract in a vehicle of soluble metallic salts. The biological test in rabbits shows a definite heterophile antibody-stimulating action.

From the recognition of the fact that animals produce antibodies against the heterophile portion of various micro-organisms,[11] it is but a short step to the deliberate use of such an antigen in the prophylaxis and treatment of disease. Experimentally, it has been observed that rabbits immunized with sheep erythrocytes are relatively resistant to various infections.[11, 12]

Heteril is capable of intensifying the natural defensive resources of the body, and thus is useful in a wide variety of infections. It is sometimes used as adjuvant therapy in combination with specific agents, but it is not a substitute for the specific serums.

Heteril is not an endocrine agent per se, but its action includes indirect endocrine benefits since, by modifying or shortening the duration of infections, the glandular system is protected against depletion.

PARATHYROIDS.—Paracalcin is a pluriglandular desiccation containing parathyroid extract, spleen, and orchic substance. It is available also in solution for hypodermic use. This formula has been used for years as a means of promoting healing in many forms of chronic ulceration. It is also a valuable supplement to injections of the standardized parathyroid hormones, such as parathormone. Paracalcin is not indicated in severe parathyroid hypofunction such as tetany, but it is an effective therapy in the lesser hypoparathyroid cases, where the fixed calcium of the serum is not appreciably altered but where the diffusible calcium is low. Paracalcin has been used as an adjuvant in the treatment of duodenal and peptic ulcer; also with possible clinical benefit in paralysis agitans and chorea, in parathyroid exhaustion of pregnancy, and in other conditions with low diffusible (ionizable) calcium as a common etiologic factor.

HEART.—Some investigators, notably Haberlandt,[13] have insisted that there is a heart hormone, although it has not been isolated. There is very little evidence in the literature that heart-muscle therapy is in extensive use. Schwartzman [14] has reported some clinical satisfaction from a muscle extract and claims that benefit was found in angina, Vaquez' angina, and intermittent claudication. In this field, pancreas-tissue extract (Panocrin-C, see Chapter IV) is very definitely of value and has largely taken the place of heart-muscle therapy.

The work of Oppenheimer [15] does not confirm the theory of a specific heart hormone, but supports the idea of

" . . . a widely distributed substance occurring in most tissues, and possessing, in adequate concentration, an augmenting action on the heart."

In 1927, following Haberlandt's interesting work, at the request of several friends we made a concentrate of beef heart muscle which is now called Myodin. Its use has been empirical, usually as adjuvant therapy in myocardial damage, but there have been many attestations to its clinical value. Since recent investigation has demonstrated a relationship between avitaminosis and heart disease, vitamin B has been added to the cardiac extract.

Of course, Myodin does not take the place of digitalis or other standard remedies, but is purely an adjuvant. The dosage is 2 capsules t.i.d. for some time and, in the presence of well-marked B avitaminosis, additional amounts of a suitable concentrate should be given.

KIDNEYS.—For more than fifty years extracts of renal tissue have been used empirically in kidney disorders, especially the toxemias of pregnancy and albuminuria. There is evidence in the literature of the rationale of this therapy, although a renal hormone has not been demonstrated. A combination of desiccated renal tissue and pancreas extract known as Glomerulin has been on the Harrower list for years. It is a useful adjuvant in several types of kidney dysfunction. The dosage is from 2 to 4 tablets at meals and at bedtime, and it is frequently an advantage to consider the addition of suitable amounts of Endothyrin (page 35).

PINEAL.—There seems to be no doubt that the pineal is a gland of internal secretion and that pineal pathology, rarely encountered, is related to essentially endocrine developments. Early experimental work demonstrated that the feeding of pineal substance to small animals hastens their growth and maturity. Twenty-five years ago W. N. Berkeley was enthusiastically recommending pineal therapy in certain classes of defective children, but his notions have fallen into desuetude. Various extracts have been made from the pineal gland, but there is little acceptable evidence of their clinical value. The extract is costly—it is said that 5,000 bovine pineal glands are required to make one pound of the finished concentrate. It is not on the Harrower list.

STOMACH.—The stomach is the source of at least two quite valuable therapeutic weapons—the digestive ferment, pepsin, and what has come to be called the "gastric hemopoietin." The former is well known and in extensive use, though it is not on the Harrower list. The latter has taken a position of secondary importance to the potent antianemia liver fractions.

THYMUS.—Thymus extracts have been prescribed empirically for many years, particularly in certain dermatoses and in arthritis. Some good results have been reported in psoriasis,[16] but the evidence is conflicting. Thymocrin, a Harrower solution, is available direct from Glendale, but does not appear on our list. There is some evidence of a growth-stimulating effect.

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13. Haberlandt, L.: Med. Welt., No. 9, 1929, iii, 307; Endokrinologie, May, 1930, vi, 335.
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OTHER GLANDULAR EXTRACTS

GLOMERULIN (Renal Co.)
Adjuvant Therapy in Kidney Disorders

Indications: Albuminuria; Nephritis; Renal Glomerular Impermeability.

Form Available: (List No. 85) **Glomerulin Tablets**—each 5 gr. contains desiccated Renal Tissue Extract gr. 2½; Total Pancreas (insulin-free) gr. 1½; milk sugar q.s. (Bottles of 100.)

Dose and Administration: Oral only: From 2 to 4 tab. four or more times a day.

MYODIN (Myocardin)

Adjuvant Therapy in Myocardial Damage

Indications: Myocarditis; Myocardial Weakness.

Form Available: (List No. 91) **Myodin Capsules**—each capsule contains 5 gr. concentrated extract of Beef Heart Muscle and 20 International Units of Vitamin B_1. (Bottles of 40.)

Dose and Administration: Oral only: 1 cap. q.i.d., at meals and at bedtime for two weeks; double dose for two weeks. Continue this variable dosage for several months as an adjuvant to digitalis or other indicated remedies.

PARACALCIN (Para-Spleen Co.)

A Compound Parathyroid-Spleen Formula

Indications: Used empirically in Chronic Infections with Ulceration; Parkinson's Disease.

Forms Available: (List No. 24) **Paracalcin Tablets**—each 5 gr. contains Spleen Extract (1:4½) gr. 2½; Parathyroid Gland gr. 1/20; Orchic Substance (1:9) gr. 1; Calcium Lactate q.s. (Bottles of 100.)
(No. 24A) **Sol. Paracalcin**—each cc. contains the water-soluble active principles of 20 gr. fresh glands in the proportions: Spleen 10, Parathyroid 1. (Packages of five 1-cc. amp.)

Dose and Administration: Oral: 1 tab. q.i.d., at meals and at bedtime, for two weeks; double for two weeks; repeat. Parenteral: 1 cc. intramuscularly daily, or every other day for one or two months.

SPLENOCRIN

A Reticulo-Endothelial Stimulant

Indications: Eczema, Urticaria, and Dermatoses accompanied with Eosinophilia; Chronic Infections.

Form Available: (List No. 154 S) **Sol. Splenocrin**—an aqueous solution of a deproteinized concentrate from the spleen, each cc. containing 40 mg. gland solids, with 0.5% chlorobutanol as a preservative. (Vials of 10 cc.)

Dose and Administration: Parenteral only: From 2 to 10 cc. intramuscularly. Give a small initial dose to test patient's sensitivity. One large injection may suffice, though several injections of from 5 to 10 cc. may be given at intervals of from three to seven days.

HETERIL

A Heterogenetic Lipo-Proteogen

Indications: Acute and Chronic Infections wherever non-specific therapy is indicated.

Form Available: (List No. 77 S) **Sol. Heteril**—a flocculent suspension containing a protein-lipid complex (Forssman's antigen) prepared from virtually deproteinized extracts of spleen and the stroma of erythrocytes in normal saline preserved with 0.01 per cent. sodium ethyl mercuri thiosalicylate. (Vials of 4 cc. and 10 cc. in packages of 10, 40, 100, and 400 cc.)

Biological Testing: A heterophile antibody-stimulating action is demonstrable in the sera of rabbits.

Dose and Administration: Parenteral only: Acute Infections—4 cc. intramuscularly every eight to twelve hours. Subacute Infections—2 cc. daily. Chronic Infections—4 cc. every three to six days.

Contraindications: Closed areas of infection without drainage. Not a substitute for specific serum therapy.

CALCISALIN (Calcium Phosphorus Co.)
Supplementary Remineralization Therapy

Indications: Many forms of clinical endocrine insufficiency, especially hypothyroidism, hypopituitarism, hypoadrenia, etc., are associated with chronic toxemias which tend to deplete the mineral reserve of the body. Although not a glandular product, Calcisalin, is a valuable adjuvant to indicated endocrine therapy and is the excipient in most of the Harrower formulas.

Form Available: (List No. 11) **Calcisalin Tablets**—each tablet of 1 Gm. contains the following: Magnesium Phosphate 2; Calcium Gluconate 8; Calcium Glycerophosphate 8; Potassium Citrate 32; Sodium Citrate and Citric Acid q.s. to make 100 parts. (Bottles of 100.)

Dose and Administration: Oral only: 3 tab., crushed, with one or more glasses of water one hour before food (i.e., on an empty stomach) twice a day.

OTHER APPROPRIATE EXCERPTS

Nothing in medicine is worth more than its yield in practice; laboratory data and theories as applied to medicine must take the crucible of the clinic, where truth and falsehood are separated.—G. W. Crile, Correspondence, J.A.M.A., Jan. 22, 1916, lxvi, 297.

Physicians are perhaps cynical because of our limited knowledge of the endocrines and the complexity that faces it, but the tendency is to optimism when it contemplates the accomplishments of the recent past with their great promise for the future.—J. C. Litzenberg, J.A.M.A., Dec. 4, 1937, cix, 1871.

Thus a conjecture long held by many was crystallized into the conviction that has given birth to the new and special subject of endocrinology which is sweeping aside many long cherished views of disease in a tidal wave as momentous as that which swept over medicine at the end of the last century upon the discovery of the bacterial origin of the infectious disorders. —Harvey Cushing, "Pituitary Body, Hypothalamus, and Parasympathetic System," 1932, page 9.

In recent years, at many clinical meetings the nihilistic point of view in regard to treatment has been actively championed. This point of view did much good by eliminating what was false and unproved, and an "intelligent scepticism" is always most valuable, but the reaction has gone too far: it has too often engendered the remark "nothing is known about that," when the statement should have been "I know nothing about that." The former remark is a pessimistic admission of defeat; the latter a challenge to investigate, to study the literature, and to utilize what is to be found therein. It is obvious in which direction lies progress.—Joseph C. Aub, Endocrinology, Nov.-Dec., 1932, xvi, 597.

Within the short period of a quarter of a century, the tone of endocrinology has been immeasurably elevated, in spite of rapid advance which would almost excuse immoderate enthusiasm. No more brilliant chapter has been added to the scroll of medical science than that contributed by endocrinologists, and yet the wisest and most conservative among them all agree that only the surface has as yet been scratched, and that what has already been accomplished merely foreshadows even richer possibilities in the future. Small wonder . . . that more and more clinicians, especially the younger men of our profession, have come to appreciate the indispensability of endocrinology in the everyday interpretation of clinical problems.—Emil Novak, Am. Jour. Obst. and Gynec., Aug., 1937, xxxiv, 237.

XI.—APPENDIX

1.—Dosage Table of Glandular Desiccations

Preparation	Aver. Dose t.i.d.	Rel. Dry to Fresh
Adrenal (total)	1/2-5 gr.	1:6
Adrenal Cortex	2-5	1:5 5
Bile Salts	2-5	1:4
Corpus Luteum	2-5	1:5
Duodenum	5-10	1:12
Kidney	5-15	1:8
Liver	5-15	1:6
Mammary	3-10	1:4.5
Ovary (residue)	2-5	1:6.5
Pancreas (total)	2-10	1:5
Pancreatin	2-5	1:8
Parathyroid	1/20-1/10	1:5.5
Pineal	1/10-1/2	1:7
Pituitary (anterior)	1-5	1:5
Pituitary (total)	1/4-3	1:5
Placenta	3-5	1:6.5
Prostate	3-5	1:6
Spleen	3-10	1 4 5
Testes (orchic)	3-10	1:7 5
Thymus	3-5	1:6 5
Thyroid	1/12-2	1 5

2. Synthetic Endocrine Principles

THIS is a day of "ersatz" and synthetic substitutes. If we cannot yet make silk purses from sows' ears, we can make them of material almost equally unpromising. However, in many instances, the synthetic is not quite so good as the natural product; for instance, the silk-worm still does a better job than the rayon factories.

Of course, the analogy does not hold for chemical progress in all fields, but it is fairly apt for synthetic hormones. Brilliant and significant as the synthetic production of pure hormone substances has been, these substances have rarely proved as therapeutically useful as natural products. Moreover, even the natural hormones may suffer from overconcentration or overpurification. Perfect purity does not necessarily mean a perfect hormone, and examples of this have been cited in previous chapters. Seventy per cent. alcohol is a better antiseptic than 100 per cent. Likewise, 18-carat gold (an alloy, only three-fourths gold) is a more useful substance than the pure metal.

The first hormone to be synthesized was epinephrine; it was made from catechol by Stolz in 1904.[1] Twenty-three years later thyroxin was synthesized by Harington [2] from quinol monomethyl ether. Both these substances had been obtained as pure crystals from glandular extracts previous to the synthesis which confirmed the configurational formulas assigned to them. Neither of these synthetics is preferred in therapy today.

Research towards obtaining synthetic insulin has been unsatisfactory. Although insulin itself has been crystallized, the synthesis is extremely difficult. As a result, the search has been for something with an insulin-like

effect. Frank [8] suggested the use of synthalin, a guanidine derivative, since it has a definite hypoglycemic action. However, because of its inconsistent action and toxic reactions it has never taken the place of insulin.

The full therapeutic utilization of most of these splendid scientific triumphs has been thwarted by one limitation or another. The superiority of crude thyroid desiccation over thyroxin has already been discussed. (See page 24.) Synthetic epinephrine is too costly. Synthalin [4] frequently causes digestive disturbances and in sensitive persons may produce liver damage. For these reasons the use of these synthetic products has been practically abandoned.

In April, 1934, Butenandt,[5] announced the preparation of progesterone from stigmasterol. Four years later Dirscherl and Hanusch [6] announced the preparation of progesterone by direct oxidation of cholestenon.

The male sex hormone was synthesized by Ruzicka [7] in 1934. First he made androsterone from epidihydrocholesterol; then in collaboration with Wettstein he successfully accomplished the synthesis of the natural hormone, testosterone, from cholesterol. The free hormone is not nearly so active as the propionic acid ester that was prepared two years later.[9]

Several synthetic endocrine principles, while apparently not identical with the naturally occurring hormones, may be similar in composition and action. One of these is desoxycorticosterone,[9] which differs from the free-occurring corticosterone in that one hydroxyl group is missing. Like progesterone, to which it is closely related, it was synthesized from stigmasterol obtained from soy-beans. Another product whose action simulates a natural hormone is dihydrotachysterol, a derivative of irradiated ergosterol. It was studied first by Holtz,[10] who found that it causes an elevation of blood calcium apparently similar to that produced by the parathyroid hormone.

Of the synthetic estrogens, diethyl-stilboestrol was recently prepared by Dodds.[11] It is not chemically identical with estrone, but is said to have two and one-half times the activity of estrone by the vaginal smear assay.

Kochakian [12] found that by some tests the natural, relatively crude male sex hormone is stronger than either the synthetic or the natural crystalline products, and concluded that

"The relatively high potency of the urine extracts is believed to be due to some factor or factors other than the known androgenic constituents."

He also refers to a report by Laqueur and associates,[13] who found that natural testosterone, the crystalline androgen isolated from bulls' testes, did not have so great an effect on the accessory sex glands of castrate rats as did slightly impure extracts.

During a discussion on the treatment of Addison's disease at the Royal Society of Medicine,[14] Levy Simpson stated that he had used desoxycorticosterone with some success. Apparently it is not a complete substitute for the natural cortex hormone, for he concluded:

"The synthetic hormone did not appear clinically to be the only constituent of the active cortical extract."

In attempting to explain two failures with desoxycorticosterone, Himsworth is reported to have suggested:

"The preparation might be toxic over a long period, but more probably the explanation was that it did not contain all the principles necessary. While cortin was reliable and safe, desoxycorticosterone was still in the experimental stage."

Jones felt that desoxycorticosterone appeared to be potent but unreliable.

It is probably too early at present to evaluate the synthetic estrins, progestin, and dihydrotachysterol, but experience with other synthetic endocrine principles illustrates the fallacy of presuming that a synthetic product is better because it is newer and purer. Often the reverse is true. Lake,[15] in report-

ing a paper that had been read by Collip before the American College of Physicians, states:

"The production of antihormones is in direct relation to the degree of purity of the hormone used; which suggests that, for clinical purposes, the less highly purified products should be more satisfactory."

Collip, who has done much research into the question of the response of the organism to concentrated hormone therapy, postulates these so-called "antihormones" as defense substances, produced by the body as a protection against excessive amounts of hormones introduced as remedies. Speaking of the purified antigrowth factor of the pituitary, he said:[16]

"Animals treated with crude anterior lobe extracts have continued to grow for longer periods and the very interesting possibility arises that the production of antihormones may be greatly modified by the degree of purity of the hormone extract used in treating the experimental animals."

With a single exception, The Harrower Laboratory offers only natural endocrine principles, practically all of them being of glandular origin. Where these are satisfactorily standardized and their potency is comparable with that of the synthetic substitutes, it appears that the natural product is preferable.

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10. Holtz, F.: Klin. Wchnschr., Jan. 20, 1934, xiii, 104.
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14. Report: Lancet, Dec. 17, 1938, ccxxxv, 1414.
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3.—Endocrine "Firsts" by Harrower

IT may be of interest to the reader to know that the following biologically standardized natural endocrine extracts were first made available in commercial quantities to the medical profession by The Harrower Laboratory:

Preparation	Origin	Date
Anabolin (Chapter V)	Liver	March, 1926
Folliculin (Chapter VI)	Graafian Fluid	August, 1926
Endothyrin (Chapter III)	Thyroid	September, 1926
Plestrin (Chapter VI)	Placenta	March, 1927
Adreno-Cortin (Chapter II)	Adrenal Cortex	October, 1929
Endoluteum, Aqueous (Chapter VII)	Corpus Luteum	September, 1930
Cortinoral (Chapter II)	Adrenal Cortex	September, 1937

Thus the house of Harrower has earned its reputation for pioneering in the production of potent, stable, standardized endocrine preparations.

4.—[illegible] Trade Names

UNFORTUNATELY, trade names are a necessity in the drug business. The first trade-mark of The Harrower Laboratory was Adreno-Spermin Co. (Reg. U.S. Patent Office December 6, 1921, No. 149,100.)

The use of this style of compound names was an attempt to avoid coined words, but in 1936 the U.S. Department of Agriculture issued this ruling:

"An article containing more than one . . . active medicinal agent is misbranded if named after a single constituent."

This is the reason for discarding many names that had been in use by us for years. Subjoined is a list of the name changes:

Adremin (formerly Adreno-Spermin Co.)
Biliselin (formerly Bile Salts Co.)
Calcisalin (formerly Calcium Phosphorus Co.)
Gerantin (formerly Gonad Co.)
Glomerulin (formerly Renal Co.)
Govarin (formerly Gonad-Ovarian Co.)
Isocrine (formerly Hepato-Splenic Co.)
Mathocrin (formerly Mamma-Ovary Co.)
Myodin (formerly Myocardin)
Pediacrin (formerly Antero-Pituitary Co.)
Prostocrin (formerly Prostate Co.)
Sydocrin (formerly Pancreas Co.)

With one exception, all these trade names are now registered in the U.S. Patent Office, and we hope that our friends are familiar with them by this time.

5.—Endocrine Units of Potency

WHEREVER possible Harrower endocrines are biologically tested and standardized in accepted units of potency. Some of the most commonly used units in endocrine standardization are summarized here:

ADRENALS: Adrenal Cortex.—Adrenal cortex products are standardized qualitatively by their ability to maintain life in adrenalectomized animals. In addition, several methods of quantitative assay have been proposed. Perhaps the most widely used are the Grollman rat unit, and the dog unit as described by Swingle.

Rat Unit (Grollman).—The amount which, when fed to adrenalectomized rats one month old (six in each test) for a week, will permit the same growth rate as that found in normal animals.

One-Half Rat Unit (Grollman).—The minimum amount of hormone which, under the foregoing conditions, allows a gain in weight of 1.5 Gm. a day for each rat, using six rats in each test. (Used in the assay of Cortinoral.)

Dog Unit (Swingle).—Minimum kg. subcutaneous dose of cortical hormone necessary to maintain normal physiologic conditions in adrenalectomized dogs for a period of ten days. The two criteria are maintenance of body weight and blood level of NPN (or urea). The dogs are previously kept on maintenance dose.

There is considerable difference of opinion about the relative value of the dog unit and the rat unit as a measure of potency. Most workers favor the rat unit. According to Cartland and Kuizenga, 1 rat unit equals about 20 dog units. (Am. Jour. Physiol., Dec., 1936, cxvii, 678.)

THYROID: Thyroideum, U.S.P., is standardized by its iodine content, the requirements being "not less than 0.17 per cent. and not more than 0.23 per cent. of iodine in thyroid combination, and must be free from iodine in inorganic or any form or combination other than that peculiar to the thyroid gland." The iodine content of Endothyrin by the same method is 0.6 per cent.

PANCREAS: Insulin (Toronto).—Standardized in international units. One unit is the equivalent of 0.125 mg. of the international standard preparation of dry insulin hydrochloride as prepared by the Medical Council of Great Britain. One mg. of standard preparation contains 8 insulin units, as provisionally defined by the Insulin Committee of the University of Toronto.

Pancreatin.—U.S.P. XI requires that "it convert not less than twenty-five times its weight of starch into soluble carbohydrates and not less than twenty-five times its weight of casein into proteoses."

Panopsin (Harrower).—Concentrated pancreatic amylotrypsin which converts not less than five hundred times its own weight of raw starch in thirty minutes and not less than ninety times its own weight of casein in one hour, following the procedures outlined in U.S.P. XI.

Panocrin-C (Pancreatic Tissue Extract—Harrower).—Each cc. represents 20 units. A unit of circulatory hormone is that amount of solution which will neutralize the effects of 0.001 mg. of epinephrine or 0.001 cc. of a 1:1,000 epinephrine hydrochloride solution.

LIVER: Hematopoietic.—The potency of some antianemia fractions is expressed as grams of liver per cc. of extract. A better method is that adopted by the U.S.P. Anti-Anemia Preparations Advisory Board, who define an injectable unit as that amount of material which, when given daily to patients with pernicious anemia, produces a satisfactory hematopoietic response as approved by the U.S.P. Anti-Anemia Preparations Advisory Board.

One oral unit is defined as "that amount of material which, when given daily to patients with pernicious anemia, has produced a satisfactory hematopoietic response . . . in the average case, material derived from about thirty times as much liver must be given by mouth to produce the same response as when given by injection."

Detoxicating—Anabolin.—Standardized in hypotensive units. One hypotensive unit is that amount of Anabolin which will give a blood-pressure lowering in a medium-sized dog equivalent to that caused by 0.083 cc. of a standard depressor solution when compared at the same time.

OVARIAN: Estrin (Estrogenic Hormone).—One international unit is defined by the League of Nations Health Organization as the specific estrus-inducing activity contained in 0.1 gamma (0.0001 mg.) of the standard crystalline ketohydroxyestrin.

Rat Unit (Allen-Doisy).—The quantity necessary to induce estrus in ovariectomized rats weighing from 120 to 160 Gm. when three injections are given subcutaneously at four-hour intervals, the sum of the three constituting a unit. Estrus is judged by the microscopic findings in the vaginal smear.

Rat Unit (Marrian).—Marrian's test is a modification of Allen-Doisy's. The material is injected into suitably sensitized spayed rats in four equal doses over a two-day period, the animals being read thirty-six hours after the last injection. Full cornification of the vaginal smear is taken as the criterion of estrus, and not less than 75 per cent. of the animals in each test must show a positive reaction. (Used in the supplementary assay of all lots of Plestrin.)

LUTEAL: Endoluteum (Aqueous).—Biologically tested by its ability to lengthen demonstrably the diestrous period in adult female white rats.

Corpus Luteum (Progestational).—One international unit is the equivalent of 1 mg. beta-progesterone. (The criterion of potency of Endoluteum in Oil.)

Rabbit Unit (Corner-Allen).—The minimum amount of an extract which, when given subcutaneously in five daily doses to a 3- or 4-kg. female rabbit that has been spayed eighteen hours post-coitum, will produce in the uterus a progestational proliferation similar to that found on the eighth day of pregnancy.

Gonadotropic Chorionic (A.P.L.) Hormone.—One rat unit is defined as the smallest amount of solution that, given in six equal subcutaneous doses for a period of three days divided into two injections each day, will mature immature female white rats 30 days old. (Used in the assay of APestrin.)

PITUITARY: Liq. Pituitarii Post.—U.S.P. XI states: "1 cc. of Solution of Posterior Pituitary produces an activity upon the isolated uterus of the virgin guinea-pig, corresponding to not less than 80 per cent. and not more than 120 per cent. of that produced by 0.005 Gm. of the Standard Powdered Posterior Pituitary, prepared as herein directed."

Thyrotropic Hormone: Guinea-Pig Unit (Rowlands and Parkes).—Defined as the thyrotropic activity contained in an amount of extract which, when given daily for five days, will cause the thyroids of immature guinea-pigs to attain a weight of 60 mg.

Adrenotropic Hormone (Moon).—Standardized in rat units, one of which is defined as the amount of hormone which, when injected in three doses over a period of three days into 21-day-old male rats, will cause an increase of 50 per cent. in the weight of their adrenals as compared with controls.

Follicle-Stimulating Hormone (Fevold).—Standardized in rat units, one of which is that amount of hormone which, when injected into immature female rats that are 21 days old at the beginning of the test, produces from 50 to 100 per cent. increase in the weight of the ovaries. Injections are made twice daily for three days, and weighings made twelve hours after the last injection.

Luteinizing Hormone (Fevold).—One rat unit is defined as that amount of hormone which, when combined with 2 rat units of female sex hormone and injected twice daily for four days into immature female rats 21 days old, will produce an increase in the weight of the ovaries 100 per cent. greater than that caused by female sex hormone alone. The ovaries must also be luteinized in contradistinction to the luteinization produced by female sex hormone alone.

Lactogenic Hormone: Rabbit Unit (Nelson).—The total amount of hormone which, when injected into pseudopregnant rabbits over a five-day period, will induce from 3+ to 4+ lactation in three out of five test animals.

TESTES: International Unit.—The androgenic activity of 100 gamma (0.1 mg.) of androsterone. (Used as a measure of the potency of Testocrin.)

Capon Unit (Gallagher and Koch).—The minimum amount of hormone which, upon subcutaneous injection, yields an average of 5 mm. increase in the length × height of the comb in at least five out of ten brown leghorn capons. (Used in the assay of Lydin.)

6.—Tests of the Endocrine Functions

MANY tests are in use to determine the functional state of the endocrine glands. An outline of those most commonly used is given here. For full details, the literature on procedure and interpretation should be studied, or complete instructions will be gladly forwarded to interested physicians on request to the Harrower Endocrine Library, Glendale, California.

ADRENALS: Blood Chlorides.—The blood usually contains from 450 to 500 mg. of sodium chloride per 100 cc. (In the plasma the concentration is from 570 to 620 mg. per 100 cc.) A decrease in blood chlorides is found in adrenal hypofunction, and in Addison's disease extremely low levels may be found. This may occur also in diabetes, fevers, pneumonia, and gastro-intestinal disorders with vomiting and diarrhea. Many other tests of adrenal function are based on the known adrenal influence on electrolyte metabolism.[1]

THYROID: Basal Metabolism.—Estimation of the basal metabolic rate is best-known test for thyroid function. It is computed by measuring the

amount of oxygen consumed by the patient after fifteen hours of fasting and rest, and corrected to allow for change in volume of the gas due to temperature and pressure. Clinically the B.M.R. is expressed as a percentage above or below the theoretical normal standard for the individual when his age, height, weight, etc. are taken into account. Ten per cent. above or below zero is considered within normal limits.

Thyroid Function Test (Harrower).—Definite, increasing doses of thyroid (U.S.P.) are given in a uniform and routine manner while a careful study and record are made of the pulse variations and other symptoms that may occur.[2] The value of the test is that it depends on the patient's response to thyroid and may be a guide to dosage as well as a diagnostic aid. Full explanations, materials, and charts will be sent gratis to physicians.

Circulating Time (Hyperthyroidism).—Two and one-half cc. of a 20 per cent. calcium gluconate solution (or 5 cc. of a 10 per cent. solution) is injected into a vein of the elbow as rapidly as possible through an 18-gauge needle. The end-point is that moment at which the patient first experiences an intense sensation of heat in the mouth. The average rate, which is increased in hyperthyroidism and slowed in hypothyroidism, is from 8.8 to 9 seconds.[3]

Cholesterol and Creatine Excretion.—The blood cholesterol tends to be high in untreated hypothyroidism, and is reduced by thyroid medication. From infancy through puberty, creatine is physiologically eliminated in the urine. Its excretion is decreased or stopped in hypothyroidism, and is normalized by thyroid therapy. The blood-cholesterol level, relationship between free cholesterol and cholesterol esters, and creatine variations in excretion offer valuable indices to the thyroid function.[4]

Impedance Angle Determination.—This test depends upon the fact that the resistance of the tissues to the passage of an electric current is reduced in hyperthyroidism. In lesser degrees of hyperthyroidism it is not so marked, and is, therefore, of little value in borderline cases.[5]

Insulin Resistance.—Latent or borderline hyperthyroidism may be diagnosed by central resistance to insulin, and is seen in some cases of goiter, both toxic and non-toxic. It may be described as an enfeeblement of the normal action of insulin in promoting sugar storage in the liver. The test is quite new.[6]

Iodine Tolerance Test.—This test was introduced by Means.[7] Frequent B.M.R. determinations are made on successive days until the figure remains approximately constant. Iodine is then administered (230 mg. daily) and the B.M.R. and clinical symptoms are carefully observed. Rapid clinical response and fall in B.M.R. accompany iodine therapy; relapse follows its omission. Valuable in doubtful and borderline cases.

LIVER: Of the many tests for liver function, probably the simplest and most reliable is the levulose test. Fifty grams of levulose is administered before breakfast, and blood-sugar levels are plotted at one- and two-hour intervals. Combined one-hour and two-hour rise in the blood sugar of more than 25 mg. per 100 cc. is considered suspicious, and more than 30 mg. as certain evidence of hepatic insufficiency.[8]

OVARY: The estrogenic content of the blood and urine during the menstrual cycle is a useful indication of ovarian function. Determination of the urinary pregnandiol is a measure of corpus luteum activity and may have some value in estimating whether a given cycle is ovulatory or anovulatory.

In addition to these tests, endometrial biopsies are extremely valuable. Estrogenic, gonadotropic, and endometrial studies may all be indicated in problem cases. A concise summary of the significance of such tests follows:[9]

"The premenstrual hormone tests were interpreted as follows: A positive estrogenic and a negative gonadotropic reaction is the normal finding. Complete absence of both the estrogenic and gonadotropic substance denotes primary pituitary failure. Absence of the gonadotropic substance with deficient estrogenic substance, or in some instances, excessive amounts of the estrogenic substance denotes partial pituitary failure. Deficient estrogenic substance with excessive amount of the gonadotropic substance indicates primary ovarian failure. The greatest value of the hormone tests is the differentiation thus obtained between primary and secondary ovarian failure. The degree of ovarian failure is best obtained by study of the endometrium."

PITUITARY: Sugar Tolerance.—This test is most frequently used as an estimate of pituitary and pancreatic function. Before breakfast 100 Gm. of dextrose is administered. (100 Gm. to adults weighing over 100 lb.; 50 Gm. to adults under 100 lb.; 25 Gm. to children.) Specimens of blood and urine are collected in a half hour, also at the end of the first, second, and third hours. These are analyzed for sugar and a curve is plotted. Important features in interpretation are height of the curve and the time elapsing before a return to normal. Using venous blood, the normal rise is considered to be less than 170 mg., and the return to normal should occur within two hours.

Most hypo-endocrine disturbances (hypothyroidism, hypopituitarism, Addison's disease) cause a flat curve with shortening. Hyperendocrine disturbances (hyperthyroidism, hyperpituitarism) cause accentuation of the curve with prolongation (lowered sugar tolerance). Diabetes mellitus shows a marked rise in the curve with slow return to normal; the reverse is true of hyperinsulinism.[10]

Pituitary Hormone Assays.—The amount of gonadotropic hormone in the blood and urine at the time of ovulation gives a valuable estimate of the gonadotropic activity of the pituitary gland.

PARATHYROIDS: The fasting level of calcium and phosphorus in the blood offer the most accurate measure of parathyroid function (low blood calcium and high phosphorus in hypoparathyroidism; reverse in hyperparathyroidism). There may be no marked disturbance in the blood calcium and phosphorus levels in mild hypoparathyroidism.[11] This condition is characterized by lowered diffusible or ionizable calcium and excessive nervous and muscular irritability, demonstrable by Chvostek's and Trousseau's signs.

PANCREAS: Hypofunction and hyperfunction of the Langerhansian cells, resulting in diabetes mellitus or hyperinsulinism, are best determined by blood- and urine-sugar estimations and the sugar tolerance test already described. Diabetes mellitus may also be characterized by lowered CO_2 combining power (acidosis) and high blood cholesterol; increased CO_2 combining power may be found in hyperinsulinism.[12]

Serum Diastase.—Hypofunction of the acinous cells results in a decreased output of digestive enzymes, which is responsible for many digestive disturbances, particularly fermentative indigestion. This apparently may be an etiologic factor also in many cases of food allergy. (See Chapter IV.) Pancreatic hypofunction of this type is accompanied with lowered serum-enzyme values, which are estimated by Oelgoetz' test[13] or Thiel's modification of it.[14]

TESTES: Estimation of the androgenic substance in the urine is the best laboratory test for testicular function.

PREGNANCY TESTS: Aschheim-Zondek.—The most reliable pregnancy test, developed by Aschheim and Zondek, is based on the presence of large amounts of pituitary gonadotropic hormone and estrin in the urine during pregnancy. The Friedman modification of this test is the most generally accepted procedure.

Intradermal Tests.—Simple intradermal tests have been found reliable in a high percentage of cases. A small amount of A.P.L. factor (APestrin—see page 72) is injected intradermally. No reaction is seen in the presence of pregnancy, but most non-pregnant women show a marked reaction.[15]

Pregnandiol Test.—According to Wilson,[16] if more than 10 mg. of pregnandiol is present in a twenty-four-hour specimen of urine, together with a history of a missed menstruation, the diagnosis of pregnancy is almost certain.

Luteal Sensitivity Test.—This procedure consists of injecting minute doses of corpus luteum hormone (Endoluteum in Oil—see page 81) intradermally. A positive reaction apparently indicates allergic sensitivity of the patient to her own corpus luteum secretion and such a patient is liable to develop hyperemesis. Desensitization is accomplished by administering corpus luteum hormone.[17]

1. Wolf, William: Endocrinology in Modern Practice, 1936, page 862.
2. Harrower, Henry R.: Med. Rec., Nov. 1, 1919, xcvi, 722.
3. Goldberg, S. J.: Ann. Int. Med., April, 1938, xi, 1818.
4. Hess, J. H.: Ann. Int. Med., Nov., 1934, viii, 607.
5. Report, Central Soc. for Clin. Res.: J.A.M.A., Jan. 18, 1936, cvi, 247.
6. Griffiths, W. J.: Quart. Jour. Med., Jan., 1939, viii, 23.
7. Means, J. H.: Ann. Int. Med., Oct., 1933, vii, 439.
8. Hurst, A.: Brit. Med. Jour., March 26, 1938, 661.
9. Kotz, J., and Parker, Elizabeth: Am. Jour. Obst. and Gynec., Feb., 1939, xxxvii, 233.
10. Wolf, William: Endocrinology in Modern Practice, 1936, page 855.
11. Cantarow, A., and Hare, H. A.: Calcium Metabolism and Calcium Therapy, 1931, page 53.
12. Wolf, William: Endocrinology in Modern Practice, 1936, page 457.
13. Oelgoetz, A. W., et al.: Med. Rec., Jan. 1, 1936, cxliii, 20.
14. Thiel, A. W. R.: Clin. Med. and Surg., March, 1939, xlvi, 119.
15. Lass, Paul M., et al.: Endocrinology, July, 1938, xxiii, 71.
16. Wilson, R. B., et al.: Am. Jour. Obst. and Gynec., Jan., 1939, xxxvii, 59; Mod. Med., March, 1939, vii, 50.
17. Finch, J. W.: J.A.M.A., Oct. 8, 1938, cxi, 1368.

7.—Current Books on Endocrinology (1929-1939)

THE Library of The Harrower Laboratory contains 1,044 books on endocrine subjects. There are also 137,000 mounted clippings and reprints in the files, as well as 368,000 cross-index and author cards. This material is always at the service of interested visitors.

Subjoined is a selected list of books on endocrinology published in the English language within the last ten years. This list has been compiled from the catalog of accessioned books in our library and, therefore, is in fairly close chronological order. Naturally, the reader will want to begin at the end.

Hertzler, Arthur E.: Diseases of the Thyroid Gland. St. Louis: C. V. Mosby Co. 1929. Pp. 286. $7.50.

Goldzieher, Max A.: The Adrenals: Their Physiology, Pathology, and Diseases. New York: The Macmillan Co. 1929. Pp. 436. $7.50.

Frank, Robert T.: The Female Sex Hormone. Baltimore: Charles C. Thomas. 1929. Pp. 321. $5.50.

Crafton, W. M.: An Outline of Endocrinology. Edinburgh: E. & S. Livingstone. 1929. Pp. 163. 6/6.

Curschmann, Hans: Endocrine Disorders. London: Oxford University Press. 1929. Pp. 188. $4.00.

Parkes, A. S.: The Internal Secretions of the Ovary. New York: Longmans, Green & Co. 1929. Pp. 242. $7.50.

Harrower, Henry R.: Practical Endocrinology. Glendale, Calif.: Pioneer Printing Co., Inc. 1931. Pp. 704. $5.00. (This is long since out of print.)
Graves, William P.: Female Sex Hormonology. Philadelphia: W. B. Saunders Co. 1931. Pp. 131. $3.50.
Mazer, Charles, and Goldstein, Leopold: Clinical Endocrinology of the Female. Philadelphia: W. B. Saunders Co. 1932. Pp. 519. $6.00.
Timme, Walter: Lectures on Endocrinology. New York: Paul B. Hoeber, Inc. Second Edition. 1932. Pp. 192. $2.50.
Engelbach, William: Endocrine Medicine. Springfield, Ill.: Charles C. Thomas. 1932. Pp. 1795. $35.00 for set of three volumes and index.
Rowe, Allan W.: The Differential Diagnosis of Endocrine Disorders. Baltimore: Williams & Wilkins. 1932. Pp. 220. $4.00.
Crile, George W.: Diagnosis and Treatment of Diseases of the Thyroid Gland. Philadelphia: W. B. Saunders Co. 1932. Pp. 508. $6.50.
Allen, Edgar: Sex and Internal Secretion. Baltimore: Williams & Wilkins. 1932. Pp. 951. $10.00.
Cobb, Ivo Geikie: The Organs of Internal Secretion. London: Bailliere, Tindall & Cox. Fourth Edition. 1933. Pp. 303. 10/6.
Hoskins, R. G.: The Tides of Life. New York: W. W. Norton. 1933. Pp. 352. $3.50.
Harrow, Benjamin, and Sherwin, Carl P.: The Chemistry of the Hormones. Baltimore: Williams & Wilkins. 1934. Pp. 227. $2.50.
Goldzieher, Max A.: Practical Endocrinology: Symptoms and Treatment. New York. D. Appleton-Century Co. 1935. Pp. 326. $5.00.
Cameron, A. T.: Recent Advances in Endocrinology. Philadelphia: P. Blakiston's Sons & Co. Third Edition. 1935. Pp. 406. $5.00.
Zondek, Hermann: The Diseases of the Endocrine Glands. Baltimore: William Wood & Co. 1935. Pp. 492. $11.00.
Langdon-Brown, Sir Walter: The Integration of the Endocrine System. Cambridge: University Press. 1935. Pp. 54. 2/–.
A.M.A.: Glandular Physiology and Therapy. Chicago: American Medical Association. 1935. Pp. 528. $2.50.
Grollman, A.: The Adrenals. Baltimore: Williams & Wilkins. 1936. Pp. 410. $5.00.
Rolleston, Sir H. D.: The Endocrine Organs in Health and Disease. London: Oxford University Press. 1936. Pp. 521. $13.00.
Bram, Israel: Exophthalmic Goiter and Its Medical Treatment. St. Louis: C. V. Mosby Co. 1936. Pp. 456. $6.00.
Wolf, William: Endocrinology in Modern Practice. Philadelphia: W. B. Saunders Co. 1936. Pp. 1018. $10.00.
Werner, August A.: Endocrinology. Philadelphia: Lea & Febiger. 1937. Pp. 672. $8.50.
Loewenberg, S. A.: Clinical Endocrinology. Philadelphia: F. A. Davis Co. 1937. Pp. 825. $8.00.
Kurzrok, Raphael: The Endocrines in Obstetrics and Gynecology. Baltimore: Williams & Wilkins. 1937. Pp. 488. $7.50.
Means, J. H.: The Thyroid and Its Diseases. Philadelphia: J. B. Lippincott Co. 1937. Pp. 602. $6.00.
Burt, Cyril: The Backward Child. New York: D. Appleton-Century Co. 1937. Pp. 694. $5.00.
British Medical Journal: The Endocrines in Theory and Practice. London: H. K. Lewis & Co. 1937. Pp. 278. $3.00.
Timme, Walter, et al.: The Pituitary Gland. Baltimore: Williams & Wilkins. 1938. Pp. 764. $10.00.
Sevringhaus, E. L.: Endocrine Therapy in General Practice. Chicago: Year Book Publishers. 1938. Pp. 192. $2.75.
Simpson, S. Levy: Major Endocrine Disorders. London: John Bale, Sons & Curnow, Ltd. 1938. Pp. 184. $2.50.